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MINIMALLY INVASIVE VASCULAR SURGERY:
THE EVOLUTION OF ENDOVASCULAR THERAPY

Michael L. Marin, Harold A. Mitty, Larry H. Hollier, and Valentin Fuster, Guest Editors

PART 2

CONTENTS

Endovascular Treatment of Peripheral Arterial Aneurysms *Nicholas J. Morrissey* 1

Endovascular Therapy for the Treatment of Arterial Trauma *Claudie S. McArthur and Michael L. Marin* 4

Combined Open and Endovascular Techniques for the Treatment of Complex Vascular Disease *Alfio Carroccio and David Spielvogel* 12

Embolization of Complex Vascular Lesions *Robert A. Lookstein and Jeffrey Guller* 17

Endovascular Treatment of Neurovascular Disorders *Aman B. Patel and David M. Johnson* 29

Minimally Invasive Vein Surgery *Steven M. Elias and Krista L. Frasier* 42

GRAND ROUNDS

A Review of Heart Failure Treatment *Gordon H. Guyatt and P.J. Devereaux* 47

GENERAL ARTICLES

Depression in Autopsy-Confirmed Dementia with Lewy Bodies and Alzheimer's Disease *Steven C. Samuels, Adam M. Brickman, Jeremy A. Burd, Dushyant P. Purohit, Pervaiz Q. Qureshi, and Michael Serby* 55

The Surgical Management of Severe Obesity *Daniel M. Herron* 63

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Veterans Affairs

In Memoriam

Sherman Kupfer, M.D. (1926–2003)
Editor-in-Chief (1991–2003)

Dr. Sherman Kupfer, our editor-in-chief, died on December 1, 2003 at the age of 77 years, after a long illness.

Brought up in New York City, Dr. Kupfer was a 1948 graduate of Cornell Medical School and subsequently began his career at Mount Sinai as an intern. He then trained with two outstanding investigators, Carl J. Wiggers, in Cleveland (in cardiovascular physiology) and Robert F. Pitts, at Cornell in New York (in renal physiology). This prepared him for a long, productive career in physiology and clinical medicine. He returned to Mount Sinai for his residency in Medicine and, after serving two years in the US Air Force as chief of medicine at their base in Newfoundland, joined the faculty and staff of Mount Sinai Hospital, and subsequently Mount Sinai School of Medicine, with which he had a long, close and continuous relationship until his death.

It is difficult to portray the full flavor of his many contributions to medicine and to Mt. Sinai in this short space. They were varied and critical to both the Hospital and the Medical School. Apart from his scientific contributions in renal and cardiovascular physiology and his clinical roles in kidney dialysis and transplantation, he held, with distinction, key administrative posts that were vital to the continued progress of the Medical Center. These roles included deputy dean, senior vice president for research and evaluation, director of the NIH-supported clinical research center, director of the artificial kidney unit, chairman of the institutional review board and research committee, and of the dean's committee for Mount Sinai's affiliated hospitals. He achieved all this while still continuing his valued scientific teaching as professor of Medicine. In recognition of his many services to the Hospital and Medical School, the Mount Sinai Alumni Association, in 1993, awarded him their highest honor, the Jacobi Medallion.

Dr. Kupfer became co-editor-in-chief of *The Mount Sinai Journal of Medicine* in 1990 and shortly thereafter became the sole editor-in-chief. He continued in this role right up to the time of his death. He had a great sense of the tradition of the *Journal*, which started in 1934 and has been continuously published since. Dr. Kupfer brought all his energies, intellect and wide medical knowledge to the *Journal*, to which he was intensely devoted. He had intimate knowledge of every facet of journal publication, in both the technical and editorial aspects. As an editor, he was especially concerned that articles in highly technical specialties be readily understood by physicians outside the specialty. This reflected Dr. Kupfer's gifts and zeal as a teacher – his eagerness to see medical knowledge disseminated widely within the profession and beyond.

Dr. Kupfer shared his devotion with his wife of many years, Adele, who was herself a teacher and who predeceased him by just a few months. He was also devoted to her and to their three children, Joel (M.D.), Kenneth and Marcia, their spouses, and their seven grandchildren.

The entire Mount Sinai community mourns the passing of Sherman Kupfer. We will miss him.

Leslie A. Kuhn, M.D.
Associate Editor
for the Editorial Staff

Endovascular Treatment of Peripheral Arterial Aneurysms

Nicholas J. Morrissey, M.D.

Abstract

Aneurysmal degeneration of peripheral arteries occurs less frequently than aortic aneurysm. While rupture is the most common complication of aortic aneurysms, peripheral aneurysms frequently cause thrombosis or embolization of the involved vessels. It has generally been accepted that most peripheral aneurysms in good risk patients should be repaired to avoid the ischemic complications of thrombosis or embolization. Endovascular repair of abdominal aneurysms has revolutionized the treatment of aortic aneurysms. Endovascular techniques have been used to treat peripheral artery aneurysms with varying success. Thrombosis of stent grafts has been a significant problem which has limited the success of this treatment. At present, endovascular treatment of peripheral aneurysms must be reserved for selective instances in very high risk patients. Until devices are developed which resist kinking and thrombosis, open surgery will remain the treatment of choice.

Key Words: Endovascular treatment, peripheral arterial aneurysm, aneurysms.

Introduction

Since the introduction of endovascular aortic aneurysm repair by Parodi in 1991(1), there has been a great deal of enthusiasm for endovascular treatment of arterial pathology. Some stent grafts for abdominal aortic aneurysm (AAA) have been approved for use in the U.S. A number are currently in various stages of development and investigation. Coil embolization of saccular aneurysms, which is generally not applicable to most cases, represents a crude form of endovascular treatment since treatment must exclude the lesion while maintaining blood flow to the tissues distal to the aneurysm. The introduction of devices and strategies for treatment of peripheral and visceral aneurysms has proceeded at a slower pace because of the relatively rare nature of these lesions along with difficulties developing smaller diameter devices which can function effectively in the peripheral vessels. Despite these challenges, endovascular treatment of peripheral aneurysms has been performed in sufficient numbers of cases to allow some analysis.

Popliteal Aneurysms

The popliteal artery is the most common site for an aneurysm of the peripheral arteries. They occur in 7.39 of 100,000 hospitalized men Patients with AAA have a 3.1% risk of also having peripheral aneurysms while patients with peripheral aneurysms have a 70% risk of having AAA (2). Popliteal aneurysms are bilateral in 50 – 70% of cases (2). While rupture of popliteal aneurysms does occur, the most common complications are thrombosis and distal embolization. The amputation rate rises dramatically for symptomatic patients undergoing repair of popliteal aneurysms when compared to asymptomatic patients (3). It is therefore recommended that aneurysms of 2 cm in diameter, or larger, be repaired electively (4 – 6). Successful stent-graft repair of popliteal aneurysms has been reported (7 – 12). Approximately 50% of cases failed and required reintervention, such as thrombolysis or angioplasty to maintain patency at one year of follow-up. A review of 7 femoral and 13 popliteal aneurysms treated with endovascular techniques was published recently (13). All aneurysms were treated with a

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Wallgraft ™ endoprosthesis. Of the 13 popliteal aneurysms treated, the one year successful exclusion rate was 100%, while primary one year patency was 69%. Using thrombolysis in cases with thrombosis of the graft, and repeat endovascular procedures in cases of stent stenosis, patency at one year was raised to 92%. No patients suffered thromboembolic complications related to the aneurysms and there were no amputations. While endovascular stent graft repair of popliteal aneurysms is possible and safe, patency, the duration of long-term is not known.

Femoral Artery Aneurysms

Femoral artery aneurysms are less common than the popliteal variety. While pseudoaneurysms are relatively common after aortofemoral reconstruction, true femoral artery aneurysms are rare. Due to the proximity of the femoral artery to the inguinal ligament, stent placement in the proximal femoral artery has had poor patency rates. Covered stents may be useful in treating aneurysms of the superficial femoral artery down to the above knee level. In the series discussed above (13), 7 femoral arteries were successfully treated with Wallgraft endoprostheses. The patency at one year was 100%. These data are encouraging but long-term follow-up is necessary before endovascular repair can be recommended as first line therapy for femoral artery aneurysms.

Upper Extremity Arterial Aneurysms

Aneurysms of the innominate, subclavian and axillary artery are rare. These lesions typically result from trauma, thoracic outlet compression or post stenotic dilatation of Takayasu's arteritis. Other lesions may represent typical degenerative aneurysm formation. Since these lesions are less common, the number of patients who have had endovascular repair for such aneurysms is few. Many of these aneurysms were due to trauma (14). Covered stents have been used with excellent initial success rates to treat traumatic pseudoaneurysms of the axillary and subclavian arteries (15, 16). Sufficient long-term follow-up data are not yet available to prove the durability of endovascular stent grafting (EVSG) repair for upper extremity aneurysms, but the results published to date (14) are encouraging. Certainly, the performance of a larger study to prove efficacy and long-term durability is warranted.

Visceral Artery Aneurysms

Lesions of the celiac, superior mesenteric artery (SMA) and their branches are less common than popliteal or femoral artery aneurysms. There are few large series (17, 18) of open treatment of visceral artery aneurysms because such lesions are rare. Splenic artery aneurysms are found more frequently (60%), followed by the hepatic artery (20%) and superior mesenteric artery (5.5%). Visceral aneurysms are often diagnosed after they have ruptured and when urgent surgery is needed to save the patient's life. When lesions are discovered incidentally or for symptoms other than rupture, the possibility of elective endovascular repair exists. Coil or thrombin embolization of renal and visceral artery aneurysms has been performed successfully (19, 20). Small stent-grafts also have seen limited success in the treatment of visceral artery aneurysms (21, 22). In poor risk patients, coil embolization of the artery and the aneurysm may be possible if adequate collateral circulation as in some hepatic artery lesions. The current status of endovascular therapy of visceral aneurysms remains limited by technical factors such as stent size, wire and catheter capabilities and aneurysm neck size. Most renal artery lesions remain better suited to open repair while mesenteric, hepatic and splenic arterial aneurysms can be treated initially by an endovascular procedure.

Summary

Advances in endovascular technology for treatment of peripheral arterial aneurysms has proceeded slowly. While device design is simple, the challenges of small vessel diameter and location of peripheral lesions near joints and branch vessels has restricted the application of endografting techniques. Endovascular treatment of aneurysms in larger vessels, in segments without branches and distant from joints seem to achieve the best results. The efficacy of endovascular treatment in preventing the long-term sequelae of thrombosis, embolization, and rupture has not been shown. As endovascular devices are developed for use in peripheral artery aneurysms, it will be necessary to evaluate them in prospective, multicenter trials with strict follow-up guidelines before their widespread use can be advocated.

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Endovascular Therapy for the Treatment of Arterial Trauma

Claudie S. McArthur, M.D.[1], and Michael L. Marin, M.D.[2]

Abstract

Several factors may limit the success of conventional operative therapy for traumatic arterial injuries. In particular, the inaccessibility of the vascular lesion, anatomic distortion, and the inherent problems associated with operating in a traumatized and often contaminated field are among these limiting factors. As a result, endovascular therapy has emerged as an important potential alternative.

This paper focuses on the application of endovascular therapy to the trauma patient, based on our experience and those previously published by other groups. Injuries to the carotid, femoral, axillary/subclavian and iliac arteries, as well as to the abdominal and thoracic aorta, have been successfully managed by stent-grafting.

Despite the potential benefits of this mode of therapy, its long-term utility will depend on our ability to overcome certain limitations associated with the technique, and on careful patient selection.

Key Words: Endovascular treatment, arterial trauma, stent-grafting.

Introduction

Arterial injury, including dissection, occlusion, pseudoaneurysm and arteriovenous fistula (AVF) formation, may result from both penetrating and blunt trauma. The success of current operative therapy for traumatic arterial injuries may be limited by several factors. The inaccessibility of the vascular lesion (e.g., due to central vessel involvement), anatomic distortion that results in venous hypertension with excessive bleeding, and inherent problems with operating in a traumatized and often contaminated field, are among these limiting factors. Furthermore, the presence of multiple trauma or severe medical co-morbidities may increase the incidence of surgical complications and mortality (1).

The use of endovascular stent-grafts to address these limitations was first introduced by Dotter in 1969 (2). Over the past 12 years, endovascular grafting has been evaluated as an alternative to conventional surgical repair in the management of aneurysms and other vascular lesions. The application of this form of therapy as well as other endovascular techniques for the management of vascular trauma offers many potential advantages. Angiography assists with the diagnosis of traumatic lesions such as intimal dissections and AVFs (3). Embolization techniques for hemostasis have been well studied and are the standard for the management of bleeding from pelvic fractures (3). In addition, endovascular techniques can be utilized to help with vascular control, as an adjunct to surgery in regions where obtaining proximal or distal control is technically difficult. The use of endovascular stent-grafting for the definitive repair of traumatic lesions has been shown to be associated with a decrease in anesthetic requirement, blood loss, and extent of dissection (4). High-velocity missiles can produce a significant amount of tissue damage, even if not suspected on initial examination due to the classically small size of the entrance and exit wounds (5). The inherent problems of graft placement in the setting of severe tissue damage, gross contamination and scar tissue formation make

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the use of a remote insertion site particularly advantageous in the trauma patient (6, 7).

At present, the largest experience with endovascular graft therapy for the management of vascular trauma has been with the treatment of arterial pseudoaneurysms and AVFs (4, 6, 8–13). Although the optimal timing of repair is still controversial (14, 15), this method is limited to the stable patient. In the setting of severe ischemia or active hemorrhage, urgent conventional operative repair is still recommended (9). Similarly, the patient with an expanding hematoma or multiple traumatic injuries may not be a suitable candidate for endovascular graft therapy. Stented grafts have been extensively studied and have demonstrated excellent technical success rates (16). In its use for arterial trauma, endovascular stent-grafting has proven safe and effective in preliminary investigations (4). This paper focuses on the specific application of this technology to the trauma patient. The discussion presents the potential benefits and disadvantages of the specific methods, reviews the current status of the field and available data, and addresses the technology's future role within the field of trauma surgery.

Techniques

Clinical experience has demonstrated a wide variety of options for device use in the treatment of traumatic lesions (4, 10, 16, 17). In their current design, stented grafts for treating traumatic arterial injuries are composed of a stent rendered nonporous by an outer covering. The covering, whether polytetrafluoroethylene (PTFE), Dacron, polyester or other material, does not appear to influence outcome (9). Some have used radially expandable, thin-walled Dacron grafts (16); others have used autogenous vein (jugular or saphenous) sutured to a Palmaz stent (16, 18). At our institution, we have used Palmaz balloon-expandable metallic stents in conjunction with thin-walled PTFE graft material to perform arterial repair of pseudoaneurysm and AVFs. Precise delivery to the site of injury is performed under fluoroscopic guidance. Heparin is used during insertion, but long-term anticoagulation has not been necessary.

An alternative device is the Corvita stent (Corvita, Inc./Schneider Corp./Boston Scientific Corp., Natick, MA) graft, which is fabricated from a self-expanding stent of braided wire. The Corvita stent-graft was the first commercially available endograft to enter into clinical trials. It has the distinct advantage of being able to be cut to the desired length in the operating room prior to loading into a special delivery sheath. The sheath has a special pusher catheter which is used for maintaining the graft in position while the outer sheath is being retrieved. The Wallgraft (Schneider-Pfizer, Minneapolis, MN) has a similar design and a polyester outer covering. Another system, the Passager Endograft System (Boston Scientific, Watertown, MA), uses a nitinol thermal-expanding stent covered with an ultrathin woven polyester fabric.

Another endograft device which has been successfully used for traumatic lesions is the Hemobahn™ graft, produced by W.L. Gore and associates (Flagstaff, AZ). This device is also fabricated from an ultra-thin ePTFE tube externally supported by nitinol wire arranged in a helical coil fashion.

Carotid Injuries

Internal carotid artery (ICA) pseudoaneurysms are often the result of a previous dissection occurring either spontaneously or in association with an identifiable traumatic episode (19). The significant risk of life-threatening stroke or hemorrhage warrants strong consideration for treatment of these lesions, even if asymptomatic (19). Although standard treatment has been open surgical management, endovascular techniques have been utilized recently to address the problem (8, 19). Conventional open repair is often technically difficult or impossible when exposure at the skull base requires mandibular disarticulation (5, 8, 19). In such a situation, endovascular repair provides a potential alternative. Several centers have reported the use of bare stents to treat such aneurysms (19–22). However, in the case of larger, wide-mouthed aneurysms (22), the aneurysms were not totally excluded by the Palmaz stents alone and continued to be at risk for rupture and embolization. Complete aneurysm exclusion with an endovascular graft may be a more reasonable option in the case of large ICA aneurysms.

Our colleagues recently described the successful use of an endovascular stented graft composed of a Palmaz balloon-expandable stent covered with a PTFE thin-wall vascular graft (Impra, Tempe, AZ), for the treatment of a 2 cm ICA pseudoaneurysm located at the skull base (8). Access may be obtained by either a femoral approach or direct operative exposure of the common carotid artery at the base of the neck. Open exposure of the proximal carotid artery allows blood flow to be arrested, thereby reducing the risk of embolization secondary to luminal manipulations. The patient remains asymptomatic on oral anticoagulation, and the aneurysm remains fully excluded.

In addition to pseudoaneurysm formation, blunt carotid injury may result in intimal dissection, for which standard therapy has been systemic anticoagulation (23). In 1997, Duke et al. reported a series of six cases of progressive dissection or pseudoaneurysm formation following blunt carotid injury (24). All six patients were successfully treated with covered stents without the use of anticoagulation.

Parodi et al. reported 8 cases of traumatic internal or common carotid artery pseudoaneurysms or AVFs treated with autogenous-vein-covered stents, the Corvita endograft, or the Wallgraft (25, 26). Parodi reported one failure related to external compression of the Palmaz stent at the level of the base of the skull (25). Determination of the potential benefit of using autogenous vein vs. a synthetic-covered stented graft in such patients needs to be addressed in a controlled study. Whether exclusion of the aneurysm will prevent future expansion and potential rupture of the pseudoaneurysm will require long-term evaluation.

Femoral Artery Trauma

With the rapid expansion in the use of interventional procedures and the rising incidence of civilian-based (noncombatant) trauma, AVFs and pseudoaneurysms of the femoral arteries have become common vascular complications. Small AVFs may resolve spontaneously, but larger fistulas do not generally have the same benign prognosis (27, 28). Currently, surgical treatment is recommended for the prevention of complications, including hemorrhage, thrombosis, compression of local neurovascular structures, venous hypertension and congestive heart failure (6). Yet, surgical repair is often technically difficult, due to bleeding secondary to venous hypertension associated with the arterialized vascular bed (6). We reported the first successful repair, in an 18-year-old youth, of a traumatic AVF caused by a bullet wound to the superficial femoral artery and vein, using a balloon-expandable, stented, PTFE-covered Palmaz stent-graft (6). At 5 months follow-up, the graft was still patent.

Subsequently, a number of groups have reported on the treatment of traumatic femoral pseudoaneurysms and AVFs, with technical success rates of 90–100% and one-year patency rates of 83–100% (4, 16, 26, 29). Although the use of covered stent-grafts has been reported for the treatment of popliteal pseudoaneurysms and AVFs (3, 26, 30), the long-term patency of the grafts and adjacent vein has not been evaluated.

Axillary/Subclavian Trauma

Penetrating axillary and subclavian artery trauma may result in the formation of a dissection, pseudoaneurysm or AVF. Post-traumatic pseudoaneurysms of the subclavian and axillary arteries are rare, and like aneurysms of other arteries, can rupture, thrombose or embolize (31, 32). Other mechanisms of injury include compression with contusion, avulsion, and traction from stretch or rotational stress (33). The surgical approaches developed to repair such lesions include clavicular resection, median sternotomy and thoracotomy, but these are each associated with significant potential for morbidity (34). The approaches require extensive dissection, often with large volume of blood loss and prolonged hospital stay.

Although the optimal management of such injuries is unclear, the role of endovascular stent-grafting for such lesions has expanded over the past decade (4, 11, 16, 26, 35–38). Parodi reported on 12 patients who underwent endovascular grafting for the treatment of axillary or subclavian AVFs or pseudoaneurysms (26). In that series, one partial failure of the main stent occurred due to an additional AVF located in a branch of the subclavian artery. The AVF was closed successfully with a detachable balloon placed into the scapular branch of the thyrocervical trunk. All cases of longstanding AVF were associated with a significant stenosis at the site of injury that required dilation prior to graft implantation. In a collective review of 18 recent cases of axillary or subclavian artery trauma managed with endovascular stent-graft therapy, a technical success rate of 94% was reported (10). Primary patency in these patients was 85% at a mean follow-up period of 18 months. Associated complication rate was 6%. Mean length of hospital stay was 3.3 days. Another group recently reported its experience with one patient with an embolizing traumatic subclavian artery aneurysm. The aneurysm was repaired with a polyester-covered nitinol stent with concomitant vein bypass of embolic brachial artery occlusion. At 24 months follow-up, both bypasses were patent (37).

Aorta or Iliac Artery Trauma

Patients sustaining blunt trauma to the abdominal aorta often do not survive, due to the impact of the direct compressive force and associated injuries. In a recent review, the mortality rate associated with blunt abdominal aortic injury was 24% (39). Injuries may include intimal disruption with dissection, intramural hematoma, pseudoaneurysms, as well as simple contusion to frank rupture (40, 41). Endovascular stent-graft repair of such injuries has emerged as a therapeutic option in the case of stable aortoiliac injuries. Most experience has been with penetrating injuries of these vessels, either iatrogenic (related to surgery or catheterization procedures), or bullet injuries (10, 12, 42). In the presence of associated injuries or hemodynamic instability, conventional open repair should be undertaken. Fifteen patients in recent reports underwent endovascular stent-graft repair of traumatic injuries to the abdominal aorta or iliac arteries — injuries that were either AVFs or pseudoaneurysms (4, 13, 16, 35). Technical success of the procedures was 100%, with primary patencies of 100% at a mean follow-up period of 10.5 months (10).

Isolated injuries to the iliac vessels have also been successfully treated with endovascular grafting (43, 44). Rupture of the iliac artery occurs in one of every 200 angioplasty procedures (45, 46). In these cases, emergent repair of an acute rupture of the external iliac artery during angioplasty by endovascular stent-graft is likely to be necessary, as reported by Formichi et al. (43). The authors obtained temporary hemostasis using balloon tamponade followed by exchange for a Cragg-Endopro-System-covered endoprosthesis to seal the injury. At follow-up more than 18 month later, the graft was still patent without endoleak.

Thoracic Aortic Trauma

Most blunt thoracic aortic injuries are caused by deceleration injuries, most often related to motor vehicle accidents (47, 48). Patients who sustain trauma to the thoracic aorta, whether blunt or penetrating, usually do not survive (49). The few patients who survive the immediate injury often develop a chronic aortic aneurysm (50, 51). Open thoracic surgery for repair of a chronic traumatic aneurysm is associated with a mortality rate of 5–18%, due mainly to bleeding, heart failure or renal failure, with associated morbidity rates as high as 50% (51, 52). In the case of acute aortic injury, the frequency of multiple traumatic injuries further increases the mortality rate (53–55). The presence of medical co-morbidities also contributes to a poorer prognosis (56).

Due to the lack of prospective data regarding the optimal management of these injuries, controversy exists as to the indications for operative therapy. Minor injuries, including mural hematoma or intimal flap, usually resolve on their own (57). Pseudoaneurysms, even small ones, rarely remain stable over time, and have a high risk of rupture, embolization, fistulization or compression of adjacent structures (57, 58). Nonoperative management can be considered only for simple lesions, for some patients with severe neurologic deficits, or for arterial injuries not actively bleeding (57, 59, 60). For these patients, antihypertensive therapy with nitroprusside or labetalol is recommended until a decision on aortic repair is reached (61). Nevertheless, Finkelmeier et al. reported that 33% of his patients with untreated chronic aortic aneurysm died of complications attributed to the aortic lesion, with 75% of deaths secondary to aneurysm rupture (51).

Endovascular stent-grafting of traumatic thoracic injuries has begun to assume a role in the management of these injuries (62–65). Using this technique, the need for aortic clamping is obviated. This could potentially decrease the incidence of paraplegia, which has been reported to occur in 4–32% of cases after surgery for thoracoabdominal aortic aneurysm (66). Although several factors have been implicated in the pathophysiology of paraplegia in thoracic aortic surgery (66), duration of spinal cord ischemia is undoubtedly a major factor (67). The endovascular approach does not allow for the reimplantation of intercostal arteries. However, in the case of nonpenetrating thoracic aortic injury, the location of the lesion is at the isthmus approximately 90% of the time (48, 68); therefore, the area of repair usually does not involve segments with branches to the spinal cord (62).

Respiratory failure is the most common complication following surgery for thoracic aortic aneurysms (69). The elimination of thoracotomy, especially in patients with existing pulmonary disease, will probably decrease the incidence of this complication, with an additional benefit in hospital cost reduction. We will probably also see a decrease in other complications, related to the decrease in operative blood loss, the minimal invasiveness of this form of therapy, and the reduced need for general anesthesia, (particularly in patients with serious risk factors for open repair).

Several limitations must be addressed. With most of these injuries occurring at the isthmus just beyond the origin of the subclavian artery, the length of the proximal neck may be insufficient for adequate fixation of the stented graft if precise deployment is not achieved. This may result in either endoleak (incomplete aneurysm exclusion) or occlusion of the upper extremity inflow. Preprocedural left-subclavian-to-carotid transposition has been useful in increasing the proximal endograft landing zone. In addition, the relative rigidity of the stent-grafts currently used limits their ability to conform to the curved aortic contour of the distal arch or proximal descending aorta (62).

Another problem that could limit benefits of a minimally invasive procedure may arise in the case of a large traumatic aneurysm, when compression of adjacent structures (e.g., mainstem bronchus) is unrelieved by simple surgical graft interposition. In such a case, removal of large amounts of intramural thrombus around a mainstem bronchus is necessary to relieve lung atelectasis (70). Furthermore, heparin is required to prevent thrombosis caused by the obstruction of blood flow related to the large delivery sheath. In the acute trauma patient with coexisting injuries, this is potentially hazardous.

To date, a number of groups have reported on their experience with endovascular stent-graft repair of thoracic aortic trauma. One group reported a single case of a previously paralyzed patient who had sustained a bullet wound injury to the descending thoracic aorta at the level of T11. The pseudoaneurysm was discovered 3 months after the injury, and was repaired using a Dacron-covered (Dupont, Wilmington, DE) nitinol stent inserted via a retroperitoneal approach to the iliac artery. Follow-up studies failed to demonstrate the presence of an endoleak or pseudoaneurysm (64). A second group reported on 10 patients who underwent repair of a traumatic thoracic aortic aneurysm (62). In their study, modified Z-stents covered with either woven polyester or expanded PTFE graft material were used to treat 10 aneurysms, 9 of them located at the level of the isthmus. In this report, three major complications were noted. One patient developed an endoleak, which was successfully treated with coil embolization. The second patient developed thrombosis of the subclavian artery, which was treated by subclavian-carotid bypass. The last patient required stenting of the left mainstem bronchus to relieve left lung atelectasis. There were no other major or minor complications, including paraplegia, embolization, respiratory failure, renal failure or myocardial infarction. Another group reported two patients with distal descending thoracic aortic pseudoaneurysms which received successful stent-graft repair (in which only the T11 intercostal artery was sacrificed by endoluminal exclusion) (65). One recent study of endovascular graft treatment of acute bleeding from traumatic aortic rupture or aortobronchial fistula in 6 patients reported a 100% success rate, with no major complications (71).

Our own recent series of thoracic aortic stent-grafting using balloon-expandable and self-expandable endovascular grafts in 14 patients included 5 traumatic injuries (72). In this series, graft insertion was technically successful in 11 of 14 patients (78%), with procedural failures related to graft migration and endoleaks. Self-expanding devices were found to be associated with greater success, most likely related to the avoidance of asystole in obtaining precise device position. There were 2 deaths, as a result of microembolization and multiorgan system failure. Average length of hospital stay was 2.9 days. The use of endovascular stent graft-repair for traumatic thoracic aortic injuries, despite significant limitations to its application, will probably be shown to be of great benefit for selected patients in future studies.

Discussion

Since Parodi's first report of the use of endovascular stent-grafting for the treatment of aneurysms (73), the use of endovascular surgery has broadened to include the treatment of arterial trauma, although experience is limited. Endoluminal grafts have been used to treat occlusive and aneurysmal arterial disease, with variable success (74). In comparison with standard operative repair of traumatic injuries, this new, less invasive method appears to be associated with less blood loss and a reduced requirement for anesthesia. Less dissection in a traumatized field is of particular advantage in the case of arteriovenous fistulas with venous hypertension, where standard surgical repair is notoriously difficult and associated with large operative blood losses in the setting of either acute or chronic traumatic injury. When successfully applied, the procedure also has the advantage of greater simplicity and decreased operative time. Vascular surgeons are increasingly faced with older patients who have severe comorbid illnesses that can increase operative morbidity and mortality; thus, the use of a minimally invasive approach becomes increasingly necessary.

Despite the potential benefits, eventual long-term utility will depend on our ability to overcome the limitations associated with this mode of therapy (75). It is assumed that the full exclusion of aneurysms will lead to the elimination of rupture potential. However, it is possible that arterial pressure that is transmitted to the thrombosed, excluded circulation will lead to eventual aneurysm expansion and rupture. The fact that a decrease in the excluded aneurysm size has been observed is encouraging (12, 16); however, rupture has been observed following stent-graft repair of an aneurysm and a demonstrated decrease in aneurysm size (76). The effects of a stent embedded in the wall of a vessel in preventing future expansion is not known (25). Long-term follow-up is necessary to determine this risk.

Another possible problem in the use of this technology is the potential for development of intimal hyperplasia at the junction of the artery and the stent-graft. The Palmaz stent has been shown to be associated with only minimal intimal hyperplasia in experimental studies evaluating stenting of occlusive or stenotic iliac lesions (77).

Difficulty in obtaining access accounts for occasional problems (25). Extending incisions and prolonging procedures or resorting to more invasive approaches often result in complications ordinarily not associated with the usual procedure.

Microembolization is a serious problem encountered with endovascular surgery. In Parodi's study (25), 3 of 4 patients who developed embolic complications died as a result. These procedures all involved technical difficulties in patients with large aneurysms. Possible reasons for the increased potential for embolization in larger aneurysms were suggested by Parodi (25). These include both negotiation of the guidewire inside a large chamber with embolic material within it, and multiple manipulations resulting from miscalculation of aneurysm length.

In addition, device limitations exist and are the focus of current investigative work. Stent compression has been reported in the case of stent-graft repair of axillary-subclavian injury (10) due to compression between the clavicle and first rib. In these situations, the use of less rigid self-expanding devices has been advocated.

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Combined Open and Endovascular Techniques for the Treatment of Complex Vascular Disease

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Abstract

In an attempt to improve the outcome following aortic aneurysm repair, there has been an increased focus on endovascular technology as a minimally invasive means of treating various vascular pathologies. Stent-grafting of aortic aneurysms is an area where a less invasive approach may decrease the morbidity seen with conventional aneurysm repair. As with other technologies, increased experience and improvements in instrument design allow for applicability to a broader population of patients. However, despite such improvements, some patients' anatomic characteristics may make endovascular repair unsuitable or too risky. When complex anatomy prohibits repair by endovascular means alone, a combination of conventional surgery and endovascular therapy may be utilized in an effort to minimalize the invasiveness. Using adjunctive surgical procedures, complex anatomy may be modified to allow for a safe and successful endovascular aneurysm repair. In this paper, we describe the modification of access vessels as well as fixation sites to facilitate the endovascular treatment of aortic aneurysms.

Key Words: Endograft, aneurysm, open surgical reconstruction, endovascular techniques, thoracic aorta, iliac arteries.

Introduction

THE INTRODUCTION of endovascular technology has provided a minimally invasive means of treating various vascular pathologies. As with any technology, user experience as well as advances in instrument design have given an increasing number of patients the option of endovascular therapy. However, various anatomic characteristics might still render a patient unsuitable or at risk for complications following endovascular therapy. While future device modifications may provide all patients with a minimally invasive option, a variety of combined surgical and endovascular approaches can now provide benefits of minimal invasiveness to a patient with complex anatomy in situations which would otherwise require more traditional invasive procedures.

The treatment of aortic aneurysms provides an excellent example of complex anatomic characteristics that may make endografting unsuitable. However, the anatomy can be modified by adjunctive surgical procedures to permit a safe and successful endovascular aneurysm repair. The description of adjunctive procedures to modify access vessels as well as fixation sites in the treatment of aortic aneurysms is the focus of this paper.

Fixation Sites

Successful placement of an endograft requires adequate fixation of the endograft above and below the aneurysm at the proximal and distal necks (1 – 5). Factors such as adequate neck length and angulation as well as thrombus and calcifications have been described as potential detriments to adequate fixation. When faced with one or more of these factors, a more suitable fixation site can be achieved by extending the graft deployment across arterial branches. Moreover, the interruption of the renal and hypogastric arteries in the cases of infrarenal aortic aneurysms, or the subclavian and visceral vessels in the case of thoracic aortic aneurysm procedures, can have catastrophic conse-

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quences. Transposition and bypass of these critical vessels can safely provide an adequate fixation site for these more complex aneurysms.

Thoracic Aortic Aneurysms

Elephant Trunk

Aortic arch repair utilizes the elephant trunk technique, where the proximal graft replaces the ascending aorta, the mid-graft supplies the arch vessels, and the distal graft extends to the descending thoracic aorta (Fig. 1). Following such a repair, aneurysmal degeneration of the descending thoracic aorta can be approached endovascularly. The use of an "elephant trunk" graft as the proximal implantation site for an endograft has been described by Fann et al. (6). In these situations, the graft material from the previous reconstruction can be utilized as a proximal neck implantation site.

Subclavian Transposition / Bypass

Insufficient length for device implantation in the proximal neck of descending thoracic aneurysms may be managed by deploying the device across the origin of the left subclavian artery. Preservation of left upper extremity perfusion can be achieved by a transposition of the left subclavian artery to the left common carotid artery prior to endovascular treatment (Fig. 2). Prior to such a transposition or bypass, however, the presence of significant occlusive disease of the carotid artery must be excluded.

Infrarenal Aortic Aneurysms

Aortouni-iliac with Femoro-Femoral Bypass

Endovascular repair of infrarenal abdominal aortic aneurysms extending into the iliac arteries with inadequate distal neck in the com-

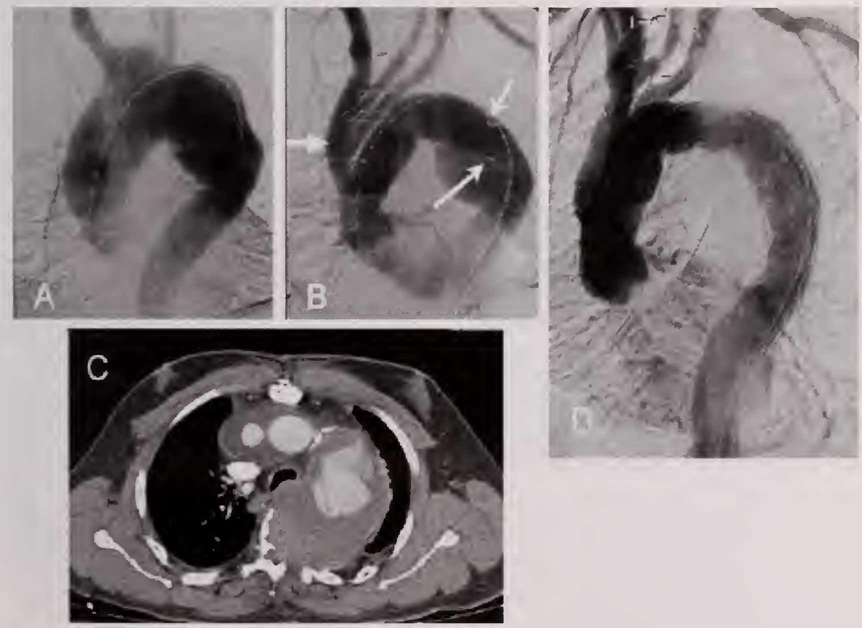

Fig. 1. **(A)** Angiogram demonstrating aortic arch aneurysm. **(B)** Aortic arch angiogram following elephant trunk reconstruction. The proximal graft begins at the aortic root. Arrow at left points to bifurcated graft originating from main aortic graft to revascularize the arch branches. Long arrows identify markers placed on distal end of graft within the aneurysmal proximal descending thoracic aorta. **(C)** Chest CT demonstrating aneurysmal descending thoracic aorta. **(D)** Aortic angiogram following stent-graft exclusion of a descending thoracic aortic aneurysm. Proximal stent-graft positioned within the previous elephant trunk graft.

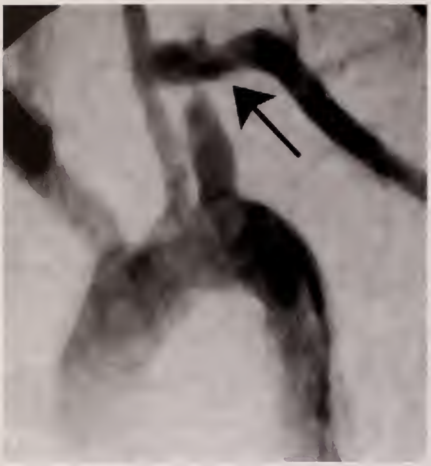

Fig. 2. Aortic arch angiogram demonstrating (arrow) left subclavian artery transposed to the left carotid artery.

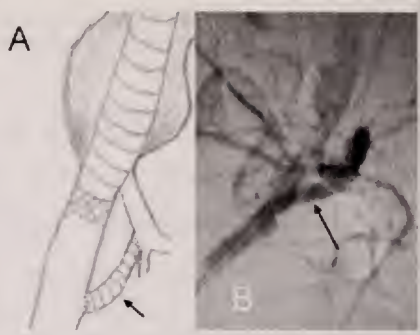

Fig. 3. **(A)** Diagram demonstrating stent-graft that extends through aneurysmal common iliac artery with planned fixation to the external iliac artery. Arrow demonstrates new anticipated position of hypogastric artery with origination from the external iliac artery. **(B)** Angiogram demonstrating hypogastric artery (arrow) being perfused by the external iliac artery following transposition.

mon iliac arteries, may be performed with an aortouni-iliac device extending to the external iliac artery after embolization of the hypogastric artery. Following placement of the uni-iliac graft, construction of a femoro-femoral bypass graft establishes circulation to the contralateral lower extremity. An occluder device is used to prevent aneurysm perfusion through the contralateral common iliac artery. This approach is not feasible when both common iliac arteries are aneurysmal. Due to concerns of pelvic ischemia, preservation of at least one of the internal iliac arteries, and thus pelvic circulation, is prudent.

Hypogastric Transposition / Bypass

Infrarenal aortic aneurysms that extend to and include common iliac artery aneurysms not only complicate the selection of an adequate implantation site, but also present a challenge to the preservation of the internal iliac arteries and pelvic vessels. A preferred method of preserving prograde pelvic arterial flow is by relocating the internal iliac artery inflow to a segment of the external iliac artery (Fig. 3), as described by Parodi and Ferreira (7).

Visceral and Renal Bypass

The various classes of thoracoabdominal aneurysms may be suitable for endovascular repair when more advanced branched endografts become available (8, 9). Alternatively, an extra-anatomic visceral vessel can be reconstructed to permit subsequent endovascular aortic grafting. As an example, extra-anatomic bypass to superior mesenteric and renal arteries can be performed. Following a brief period of recovery, the thoracoabdominal aneurysm can be excluded with a stent-graft, allowing continued perfusion of the renal and visceral vessels (Fig. 4).

Access Vessels

Passage of an endograft delivery system for aortic aneurysm repair routinely utilizes the iliac arteries. Despite improvement in devices, such as decreasing diameter and increasing flexibility, it is not uncommon to identify arteries that are stenotic, calcified and tortuous, thus restricting the passage of a device (1, 5, 10, 11). Occasionally, force utilized in overcoming these restrictions may result in arterial dissection, thrombosis, rupture, and failure to pass the device (12, 13). In such situations, alternative options may include endarterectomy, traction, and placement of a side arm conduit.

Endarterectomy

In focal, short segment, iliac artery stenosis, a simpler treatment modality is balloon angioplasty, which can sufficiently dilate the vessel to allow the device to safely traverse the lesion.

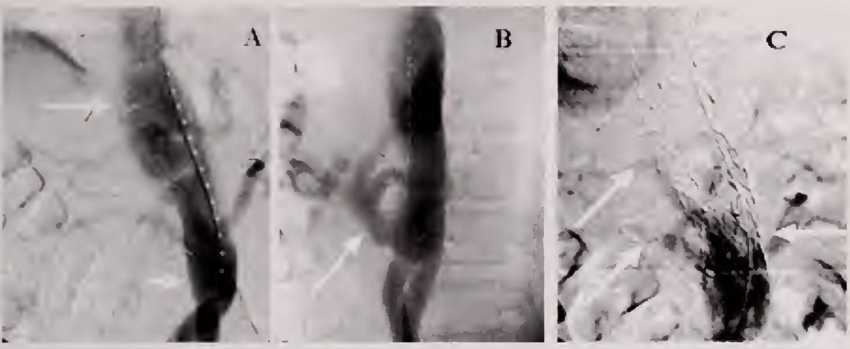

Fig. 4. (A) Aortic angiogram in a patient with previous infrarenal aortic aneurysm repair. Small arrow indicates previous infrarenal aortic graft. Large arrow indicates aneurysmal aorta within the visceral segment. **(B)** Angiogram of the same patient with arrow demonstrating a bifurcated graft with additional side branches originating from previous infrarenal graft, revascularizing bilateral renal arteries and superior mesenteric artery. **(C)** Angiogram revealing stent placed across the visceral segment, and visceral and renal branches perfused by graft.

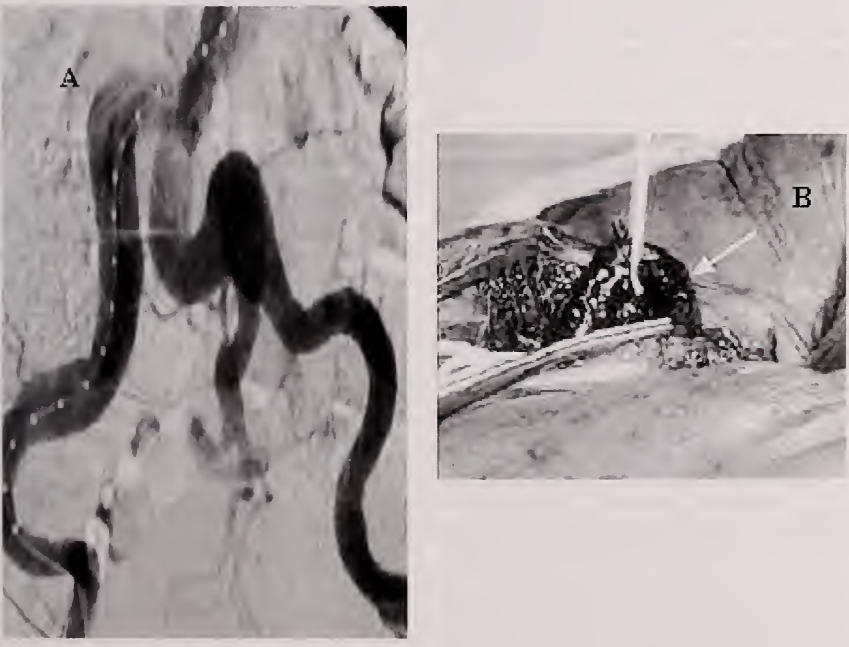

Fig 5. (A) Pelvic angiogram demonstrating tortuous iliac arteries. **(B)** Photo of groin dissection with arrow demonstrating external iliac artery, following its mobilization and traction to straighten vessel and facilitate device insertion.

Frequently, however, the iliac arteries are diffusely stenotic. In diffuse, multisegment, iliac artery stenosis, closed endarterectomy can be performed with multiple balloon dilations throughout the diseased segments. Atherosclerotic debris can then be withdrawn and extracted from the femoral arteriotomy site.

Endoluminal Conduits

Multisegment iliac artery stenosis with long, circumferential, nearly occlusive disease can benefit from intraluminal iliofemoral bypass grafts (14). These endoluminal conduits permit more aggressive dilation of a long stenotic segment of the iliac artery. This maneuver eliminates the risk of iliac artery rupture by aggressive angioplasty, because the intraluminal bypass graft protects the severely diseased vessel.

External Side Arm Conduit

The most serious disease of the iliac arteries is a combination of severe occlusive disease with calcifications and tortuosity. In these situations, the wiser choice may be avoidance of the entire diseased iliac segment. Navigation of the device can be accomplished via an extraluminal iliac side arm conduit originating from a proximal undiseased segment. This conduit can be constructed with a retroperitoneal approach. The bypass graft is then removed after endovascular aneurysm exclusion by the stent-graft.

Straightening / Traction

In calcified arteries with significant tortuosity, digital dissection allows full exposure and straightening of the redundant external iliac artery, thus decreasing the potential risk of perforation by the delivery system (Fig. 5). Once mobilized, the redundant and tortuous segment can be excised.

Summary

Combining surgical and endovascular techniques facilitates treatment of some aortic aneurysms with complex anatomy. Such an approach may also decrease possible iatrogenic injuries. Future device technology may allow some of the abnormalities to be managed solely by endovascular means.

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Embolization of Complex Vascular Lesions

Robert A. Lookstein, M.D., and Jeffrey Guller, M.D.

Abstract

Embolization, first described nearly a century ago, has recently emerged as a durable first-line treatment of many vascular conditions particularly in the field of endovascular surgery. As technological advancements allow easier and safer access to small and remote lesions, embolization is being utilized more frequently to treat difficult lesions. This technology has been used most extensively in the treatment of abnormal arteriovenous communications, where it has emerged as a first-line therapy. Recently, the application of these techniques to treat visceral artery aneurysms has been explored, with encouraging results. The endovascular therapy of aortic aneurysms has revealed numerous other applications for embolization therapy, including the treatment of iliac artery aneurysms and of failed aneurysm exclusion or endoleak. Embolization offers a minimally invasive treatment for lesions which have traditionally been considered inoperable, as well as those requiring extensive surgical resections and/or reconstructions that are associated with high morbidity.

Key Words: Embolization, endoleak, aneurysm, arteriovenous malformation.

Introduction

"EMBOLIZATION" means the intentional occlusion of a vessel by the introduction of some foreign material. This technique has been used extensively to occlude vessels in the last few decades as an alternative to traditional therapy or when traditional therapy has failed. Recently, embolization techniques have been employed more broadly and with greater precision and ease. As a result, this "last resort" technique has quickly evolved into first-line therapy for many complex clinical conditions. In this article, the specific role of this technology for the endovascular specialist will be reviewed, with attention to its use as an alternative to open surgery for the treatment of complex vascular lesions such as arteriovenous malformations, arteriovenous fistulae and visceral artery aneurysms, and as a perioperative adjunct to the endovascular treatment of aortic aneurysms.

History

Embolization has only recently attracted interest for the treatment of vascular lesions, but the technique was first described almost a century ago. In 1930, Brooks described injecting a fragment of muscle attached to a silver clip into the internal carotid artery (1). Lussenhop and Spence, in 1960, injected spheres of methyl methacrylate into the surgically exposed common carotid artery of a patient with an arteriovenous malformation fed by the middle cerebral artery (2).

Developments in catheter technology and embolic agents in the 1970s initiated the recent interest in embolization techniques. The availability of pre-shaped catheters and coaxial systems permitted the subselective placement of catheters. This advancement in turn made possible the selective delivery of embolic agents. In 1974, Lin et al. reported injecting silicone tubing through lumens only slightly larger than the embolization material (3). Later that year, Serbinenko described the use of detachable balloon catheters for embolization (4). Zanetti and

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Sherman introduced the tissue adhesive isobutyl 2-cyanoacrylate in the United States in 1972 (5). Carey and Grace described gelfoam particles as embolic agents in 1974 (6). In 1975, Gianturco created the wool coil, which after subtle modifications is still in widespread use at present (7). Microcoils soon followed, allowing for the placement of coils through microcatheters. The Guglielmi detachable coil is a recent advancement in coil technology involving the introduction, through a microcatheter, of a coil attached to a guidewire that may be detached after the passage of an electric current through the guidewire to dissolve the attachment. This allows for the repositioning of the coil after leaving the catheter and the possibility for optimizing coil deployment (8). All of these devices have a place in embolization therapy and will be discussed as they relate to the clinical entities presented here (Fig. 1).

Since the entire spectrum of embolotherapy is fairly large, the discussion here will be limited to embolization of visceral artery aneurysms, embolization-ablation therapy of abnormal arterio-venous communications, and embolization related to the endovascular repair of abdominal aortic aneurysms.

Visceral Artery Aneurysms

A rare clinical entity, visceral artery aneurysm (VAA) remains a difficult, often catastrophic diagnostic problem. Almost 25% present already ruptured, which can be fatal in nearly 10% of these patients (9). The symptoms, natural history, and outcome of visceral artery aneurysms depend on the vessels involved. The most common sites are the splenic, hepatic, superior mesenteric, gastroduodenal, and pancreaticoduodenal arteries. Splenic artery aneurysms account for almost 60% of all splanchnic aneurysms. Causes include medial degeneration with superimposed atherosclerosis, portal hypertension, infection, fibromuscular dysplasia, trauma, and pancreatitis. It is important to mention that splenic artery aneurysms are also associated with pregnancy with a significant associated rate of rupture in the third trimester. As a result, other studies (10) have advocated aggressive treatment of these lesions in this specific population. Hepatic artery aneurysms usually are secondary to some form of trauma. Superior mesenteric artery (SMA) aneurysms are typically mycotic in origin.

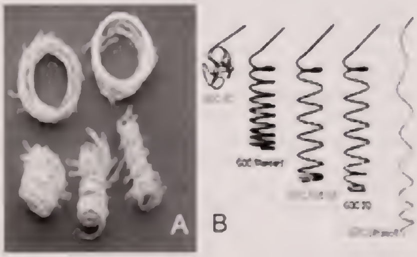

Fig. 1. **(A)** Embolization coils with Dacron fibers available in sizes ranging from 3 – 12 mm in diameter. Photograph reproduced with permission from Cook (Bloomington, IN). **(B)** Guglielmi detachable coils (GDC). Photograph reproduced with permission from Boston Scientific (Fremont, CA).

Traditional therapy consisted of surgical management with aneurysm repair and resection. Today, endovascular embolization techniques offer a safe alternative that has shown excellent short-term success. There are a limited number of published reports (11 – 14) regarding embolization of visceral artery aneurysms. Most series report on the use of coils for the procedure or a combination of coils and a liquid agent (Fig. 2).

Carr et al. reported on another single-center experience with 37 patients with VAAs (11). Seventeen patients underwent surgery, 12 had transcatheter embolization, and 8 were observed. Only poor surgical candidates were referred for embolization. All embolizations were successful, although several required repeat interventions. One patient who underwent embolization of a splenic artery aneurysm had a small post-procedure splenic infarct which resolved spontaneously. The authors went on to comment that embolization is quickly becoming the treatment of choice for these lesions in all patients. Advantages include precise localization of the aneurysms, better assessment of collateral flow, lower risk to the patients, and easier access to lesions for which surgical exposure would be difficult (11). Other authors have advocated the use of embolization rather than surgical repair as a first-line therapy for hepatic artery pseudoaneurysms, because of the decreased morbidity associated with the former procedure (12).

Gabelman et al. in 2002 reported a single-center, 10-year experience with 25 patients that demonstrated a 92% initial success rate with coil embolization. Long-term follow-up showed only one recurrence after 12 months. It is important to note that these patients must be followed with serial imaging to document success

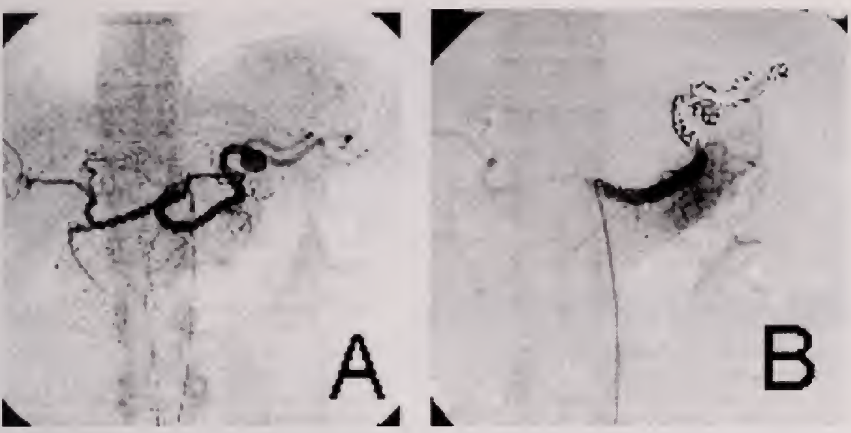

Fig. 2. **(A)** Cross-sectional imaging of splenic artery aneurysm in a 47-year-old female with hypertension. Selective celiac arteriogram demonstrates an aneurysm in the mid-portion of the splenic artery. **(B)** Selective splenic artery angiogram shows no flow into the aneurysm following coil embolization.

of the procedure and to monitor for future recurrence (13). Pilleul and Dugougeat showed the value of follow-up imaging in identifying incomplete embolization in 4 out of 18 patients treated in their series (14).

With the more widespread use of radiologic imaging, visceral artery aneurysms are being detected with increasing frequency. Because rupture of these lesions is associated with significant mortality and morbidity, treatment of asymptomatic patients is becoming a more prudent method of treatment. Endovascular embolization offers a low-risk alternative, especially for high-risk patients.

Abnormal Arteriovenous Communications

Vascular malformations are currently one of the most challenging conditions to diagnose properly and treat effectively. Because these lesions are relatively rare, few physicians have adequate experience with them.

The most important step in the management of patients with this condition is to properly diagnose and classify the lesion. This will in turn can give a patient realistic treatment options and expectations. Vascular malformations can currently be classified into four major categories:

- hemangioma
- arteriovenous fistula
- arteriovenous malformation
- venous malformation (15).

This classification can reliably differentiate between lesions with different treatment options and differing prognoses.

Hemangioma

A hemangioma is a benign vascular neoplasm, classically diagnosed in infancy. This lesion is characterized by a proliferative phase that is usually followed by spontaneous involution. Hemangiomas occur in infancy in almost 10% of the population. They may be present at birth or soon after and may be multiple in up to 20% of cases. These lesions are more frequent in females (15). Clinically, these lesions may begin as small, red discoloration and can rapidly proliferate to eventually show ulceration, bleeding, or infection. The lesions frequently involute in the majority of cases by the beginning of adolescence. Any residual discoloration can be readily treated by plastic surgery (16).

Arteriovenous Fistula

An arteriovenous fistula (AVF) is a direct communication between an artery and a vein. These lesions are usually acquired as a result of trauma. It is crucial to understand the physiology of these lesions in order to plan treatment. The basic architecture is that of a low-pressure sump. The flow through the fistula depends on the size and length of the communication. This connection will classically enlarge over time, first with hypertrophy of the feeding vessel and finally with hypertrophy of the draining vessel. Whenever the resistance in the venous outflow is less than that of the distal arterial bed, as is generally the case, then arterial flow to the tissue may be insufficient to sustain tissue viability. This will manifest itself as distal ischemic changes, claudication, skin and muscle atrophy, and even gangrene. Extensive collateral networks typically accompany arteriovenous fistulae to supply the distal tissues. This is why simple interruption of the feeding artery will not close down the fistula. Other physiologic changes that can occur include venous hypertension and venous insufficiency, which can progress to changes seen in a left-to-right shunt, such as high-output heart failure.

Treatment of the condition must aim at occlusion of the fistula with preservation of distal flow. In many instances, especially, those related to trauma, the best results for treatment of these lesions still depend on surgical repair. This is certainly the case in short, side-to-side extremity fistula. At present, endovascular grafts can be used in limited settings but are not ideal for treating distal lesions or lesions located next to joints. For those lesions that are difficult to treat surgically due to complex anatomy or difficult access, embolization may be the initial treatment. The embolization procedure is directed at occluding the fistula or at isolating the artery that is feeding the fistula (Fig. 3). The choice of material will usually depend on the specific setting, but typically will consist of large permanent agents such as coils or detachable balloons (17) (Fig. 4). Particulate or liquid agents are not routinely used for large lesions, due to the risk of shunting and resultant embolization of the pulmonary circulation. After embolization, arteriovenous fistulae are considered cured and recurrences is rare. Improper embolization can turn a readily treatable lesion into a very complex one that may ultimately require surgical repair.

Arteriovenous Malformations

Arteriovenous malformations (AVMs) are congenital anomalies that result from a focal failure of vascular differentiation *in utero* between the fourth and tenth weeks of development. These are typically isolated lesions, which are not genetically transmitted. Depending on the size and location, these lesions can be asymptomatic and undetected or can be significant clinical problems. AVMs can occur anywhere in the body but have "predilections" for specific sites, including the central nervous system, the pelvis and the lower extremities. If the lesion is accessible for physical examination, it will present as a pulsatile, non-tender mass. The draining veins can be quite prominent and the presenting symptom can often be venous hypertension in an affected extremity, with skin thickening, edema and venous ulcera-

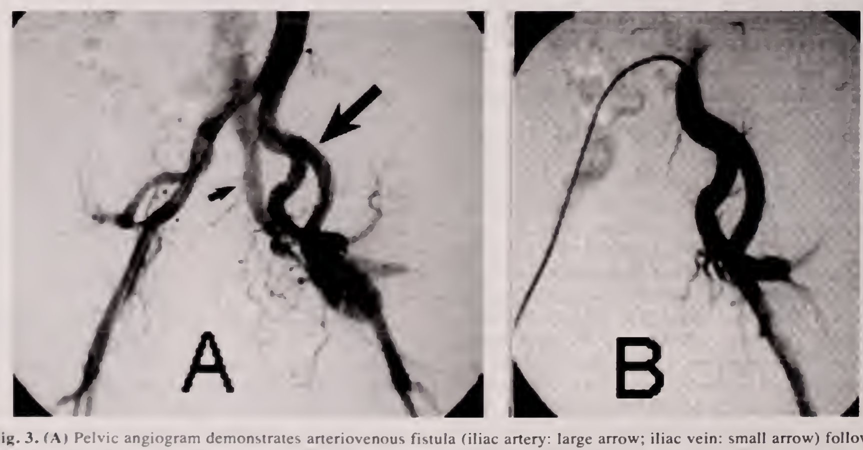

Fig. 3. (A) Pelvic angiogram demonstrates arteriovenous fistula (iliac artery: large arrow; iliac vein: small arrow) following transgluteal pelvic lymph node biopsy. **(B)** Following coil embolization of the fistula, an angiogram from the left common iliac artery demonstrates no arteriovenous shunting.

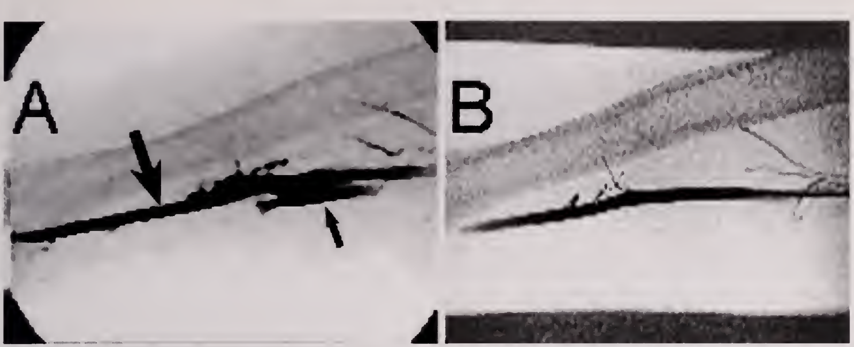

Fig. 4. (**A**) Angiogram of the brachial artery (large arrow) shows a traumatic arteriovenous fistula which occurred following placement of a peripherally inserted central catheter (PICC) line (small arrow: brachial vein). (**B**) There is no flow in the fistula after placement of a single Guglielmi (GDC) coil in the fistulous tract.

tion. When limb lesions present in childhood, limb length can be affected, usually by overgrowth. Generalized cardiovascular effects from congenital AVMs are quite rare. These lesions tend to grow slowly, but rarely some lesions can show periods of rapid enlargement. This classically occurs following a change in the hormonal environment or after unsuccessful surgical or radiological treatment. The first scenario is classically seen in female patients following menarche or pregnancy. The second scenario occurs when a stable lesion is treated resulting in recruitment of new collaterals. This will usually occur following ligation or proximal embolization of feeding arteries (16). Cross-sectional imaging has become the standard modality to properly diagnose these lesions and plan treatment. CT angiography (CTA) and magnetic resonance angiography (MRA) can demonstrate the true extent of the lesion and show the relationship of the lesion to surrounding structures. These imaging studies can also serve as a baseline, which can be repeated after treatment to monitor resolution or progression. Diagnostic angiography is not routinely performed in these cases, but can give detailed depictions of the vascular anatomy, including the demonstration of enlargement and tortuosity of feeding arteries, a dense nidus of malformation and early opacification of draining veins. Most malformations show one primary feeding artery with multiple small secondary feeders. When only the primary feeder is occluded, the secondary feeders will be recruited to supply the nidus.

AVMs are notoriously refractory to treatment. It is well known that these lesions can rarely be resected completely without tremendous blood loss and serious risk to the patient (18). Preoperative embolization can in certain instances convert an unresectable lesion into a resectable one. At present, transcatheter embolization has a primary role in the management of these lesions. Although recent technological advances in this field have made catheterization of these lesions less technically challenging, this must be tempered by the fact that improper embolization can worsen a previously symptomatic lesion. Risk and long-term results must always be presented to the patient. Complete cures are rare, and as a result, asymptomatic lesions should not be interfered with, for fear of complicating the situation. Both the treating physician and the patient must be realistic about the possibility of repeated future interventions. Each patient should be treated by a team that includes radiologists, vascular surgeons, plastic surgeons, orthopedists, and anesthesiologists.

Many embolization materials are available for the treatment of these lesions. All of these materials have been reported in the literature. With recent technological advancements, two agents have emerged as the choices for use in this setting: liquid adhesives and absolute alcohol. They have become popular because it is possible to deposit these agents solely in the nidus and minimize any damage to surrounding vessels and tissues. The liquid adhesives isobutyl cyanoacrylate (IBCA) and n-butyl cyanoacrylate (NBCA) have become the first line of therapy at many centers (16). These agents polymerize on contact with ionic material such as blood. They can be delivered through microcatheters into a vascular malformation and form a cast of the multiple small vessels near the nidus of the malformation. Although casting of the entire nidus is the goal, complete obliteration is often not achieved.

Other authors have popularized the use of absolute ethanol for the treatment of arteriovenous malformations (19). Ethanol ablation therapy can be performed either by the transcatheter technique, introduced as close to the nidus as possible or by direct puncture of the lesion. Ethanol induces thrombosis by denaturing blood proteins, dehydrating vascular endothelial cells and precipitating their protoplasm, denuding the vascular wall totally of endothelial cells, and segmentally fracturing the vascular wall to the level of the internal elastic lamina. The combination of these events causes an acute thrombosis. Advocates of this agent state that it destroys the lesion being treated by obliterating the vascular wall. This is a permanent treatment, whereas the liquid adhesives have had isolated reports of recanalization. The proponents of adhesive embolization discount alcohol therapy as being too caustic, with a relatively high incidence of skin or mucosal sloughing following treatment (16).

Pulmonary AVM. These lesions are treated even if the patient is asymptomatic. The risk of these lesions is an enhanced physiologic right-to-left shunt, which can result in hypoxia or a paradoxical embolus resulting in stroke or brain abscess. These lesions, which are classically treated with detachable balloons or coils, are not true AVMs in that they do not recruit new collateral feeders. As a result, occlusion of the pulmonary arterial feeder usually is curative. Complete embolization of the feeding vessel has been shown to be curative in almost 90% of cases, with the remainder easily treated by secondary procedures. Long-term follow-up has shown excellent durability of this procedure when either agent (coil or balloon) is used (20) (Fig. 5).

Renal AVM. These lesions can be asymptomatic for long periods of time and then present with significant hematuria. Classically, they are found in the right kidney of adult females. Embolization is now considered first-line therapy for them, as it produces excellent results (21). The procedure can be performed with either coils or a liquid agent. We prefer the use of liquid adhesives and have found them to be extremely safe and durable (Fig. 6).

Extremity AVM. These lesions are among the most difficult to treat. Because they often interfere with function of the limb, it is difficult to predict preoperatively how the embolization of the lesion will affect the extremity involved. These lesions are rarely treated completely, and more often than not they will require repeat procedures and ultimately surgery. It is imperative not to attempt proximal ligation or embolization of these lesions, because this can make future procedures all but impossible. Long-term follow-up of embolization of extremity AVMs suggests that better results are obtained from the treatment of upper extremity

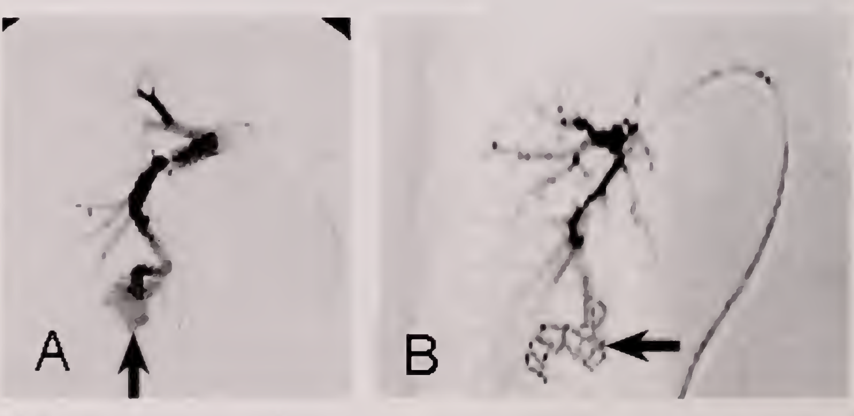

Fig. 5 **(A)** Right pulmonary angiogram shows a pulmonary AVM (arrow) arising off the right posterior basal artery. **(B)** Following coil (arrow) embolization, there is no flow in the AVM.

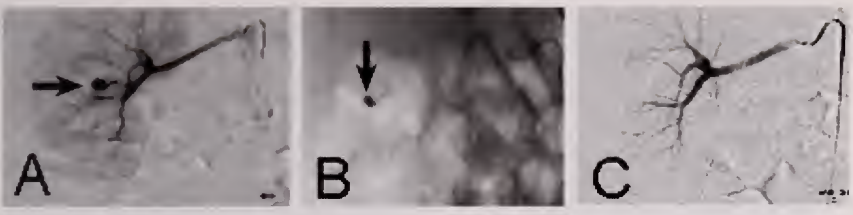

Fig. 6. (A) Right renal artery AVM (arrow) in a 27-year-old pregnant female with gross hematuria. (B) Following embolization with glue, there is a cast (arrow) of the AVM. (C) Post-embolization angiogram shows no flow in the AVM.

lesions than from treatment of lower extremity lesions (22). The lower extremity lesions appear to ultimately lead to limb loss in a majority of patients. Embolization may be able to palliate the symptoms of these patients for a period of time, but ultimately a majority of AVMs recur. This is yet another reason to use caution and realistic expectations in the treatment of these lesions (Fig. 7).

Pelvic AVM. These lesions are also quite difficult to treat. They present classically with vague symptoms including pain, mass effect and hemorrhage. Embolization of these lesions offers a minimally invasive option that has little or no morbidity and has been shown to have excellent long-term results (23).

Venous Malformations

Venous malformations, ranging from anomalies of venous anatomy to focal cavernous lesions, are relatively common. As with other vascular malformations, these are not neoplastic lesions and generally show growth commensurate with growth of the individual. Cavernous malformations can occur anywhere in the body and are composed of irregular venous spaces with slow flow under low pressure. When they are close to the skin surface, they are characteristically bluish in appearance and demonstrate a soft, nonpulsatile consistency. They can be actively emptied by manual compression or passively by elevation of the affected part. Conversely, they can become engorged when they are in a dependant position and can be quite disfiguring in appearance. These lesions are not tender unless there is superimposed acute thrombosis. Very superficial lesions can demonstrate skin thinning or even breakdown with resultant bleeding (16).

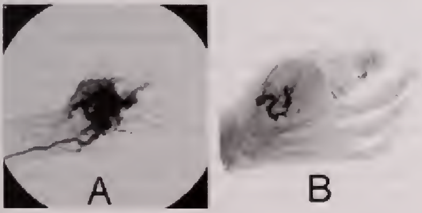

Fig. 7. (A) AVM at the left wrist in a 22-year-old female who had undergone radial artery ligation at another institution. (B) Following embolization with glue, a second digit had to be amputated.

Again, MRI/MRA is extremely valuable in delineating the true extent of the lesion, which may involve a much larger territory than is evident clinically. Arteriography is usually non-revealing. Standard venography often fails to show any filling of the lesion from normal venous structures. Direct puncture or closed space venography is a more effective technique for outlining these lesions. When the capacity of the lesion is reached, opacification of the small draining veins is usually observed, with eventual drainage into the normal venous system. This direct puncture technique is also used for treatment. Direct puncture embolization is a simple technique that has proven effective in treating venous lesions. After closed space venography, usually performed through a sheathed needle, the lesion is allowed to empty passively. The lesion is then partially refilled with a solution of contrast and absolute ethanol. The alcohol is left in place causing clotting of the blood and damage to the vascular endothelium lining the venous spaces. Signs of thrombosis will persist for 2–3 weeks and shrinkage will be seen 6–8 weeks following treatment. Depending on the anatomy and size of the lesion, multiple puncture sites may be needed as well as multiple treatments over time (Fig. 8).

Sclerotherapy alone or in combination with surgical resection has shown excellent pallia-

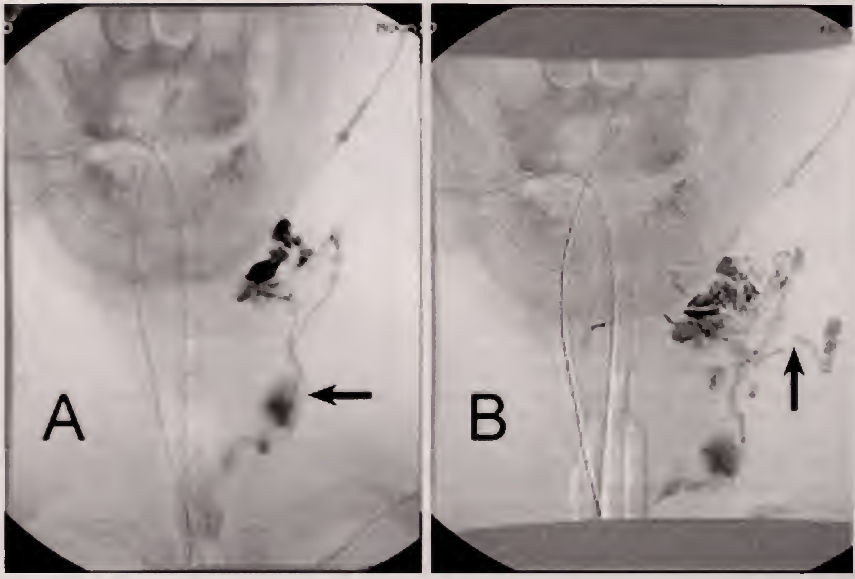

Fig. 8. **(A)** Direct puncture venogram of a venous malformation in a 23-year-old male reveals a large vein (arrow) draining centrally into the chest. **(B)** Following alcohol ablation, the capacity of the malformation is decreased. A new draining vein (arrow) is now apparent This will be sclerosed later.

tive results and is widely regarded as the preferred mode of therapy (24).

Embolization to Facilitate Endovascular Repair of Abdominal Aortic Aneurysms

Hypogastric Artery Embolization

Endovascular repair of abdominal aortic aneurysms has rapidly gained acceptance as an alternate form of treatment for patients at high risk with traditional open repair. Originally, one limitation to the procedure was the co-existence of common iliac artery aneurysms. Parodi described a technique to circumvent this obstacle, in order to offer more patients the option of endovascular repair (25). This technique involved extension of the iliac limb of the device down to the external iliac artery after the origin of the internal iliac artery had been coil embolized. This would prevent a future endoleak from reversal of flow in the hypogastric artery and back-up into the aneurysm sac. For common iliac aneurysms, the origin of the hypogastric artery would be embolized, whereas for true hypogastric artery aneurysms the entire vessel would be embolized, including anterior and posterior divisions, as previously described (26) (Fig. 9).

Numerous studies have shown not only the safety of this procedure but also its durability. Yano et al. (27) reviewed their experience with 103 internal iliac artery embolizations and showed an incidence of pelvic ischemia of approximately 20%, including 12 patients with buttock claudication, 9 patients with new-onset impotence, and 1 patient with fulminant visceral ischemia. Criado et al. (28) reviewed a series of 39 patients who underwent embolization of one or both hypogastric arteries. The post-procedure complication incidence was 1 patient with impotence and 5 patients with buttock claudication. No patients had severe ischemic complications. Recent studies have looked at the risks associated with bilateral hypogastric artery embolization. Engelke et al. (29) reviewed their experience comparing the results of simultaneous bilateral embolization with sequential bilateral embolization. Their study reviewed 16 patients and showed early complica-

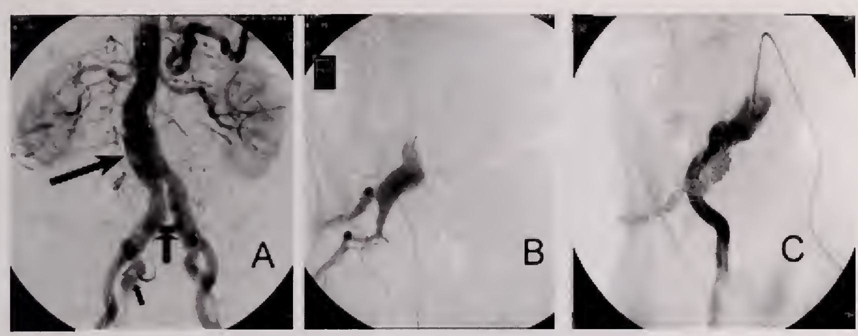

Fig. 9. **(A)** Flush aortagram shows an infrarenal abdominal aortic aneurysm (large arrow), bilateral common iliac aneurysms (medium-sized arrow), and a right hypogastric artery aneurysm (small arrow). **(B)** Selective right internal iliac angiogram shows the extent of the hypogastric aneurysm. **(C)** Following coil embolization, there is no flow in the right hypogastric artery.

tions, including an 18% incidence of buttock claudication and 6% incidence of impotence. It also showed a reduced complication rate in the simultaneous group (12.5%) as compared to the sequential group (50%). Razavi et al. reported a 57% incidence of symptoms including claudication and impotence following bilateral hypogastric artery embolization (30).

Endoleak Embolization

One of the most common complications of endovascular aneurysm repair is incomplete exclusion of flow in the aneurysm sac, which has been given the descriptive term “endoleak.” This describes the presence of blood leaking into the aneurysm sac around an endovascular graft. Endoleaks have been classified according to their origin and their direction of flow. Type 1 leaks are the result of an incomplete seal at the proximal or distal attachment sites. Leaks through occluder devices related to aortomonoiliac devices are also considered type 1 leaks. Type 2 leaks are the result of retrograde flow in aortic side branch vessels back into the aneurysm sac after stent graft implantation. The most common sites for type 2 endoleaks are the inferior mesenteric artery and the lumbar arteries. Endoleaks are regarded as a failure of the endovascular aneurysm repair procedure and should be occluded to prevent pressurization of the sac, resulting in aneurysm enlargement and possibly rupture (31). Many authors have agreed that type 1 leaks are probably more dangerous than type 2 leaks and should be treated on an urgent basis. Type 2 leaks are considered more benign and have often been shown to close spontaneously. As a result, type 2 leaks are treated only if they remain patent and are associated with aneurysm enlargement (32) (Fig. 10).

Many techniques have been described to treat endoleaks, including embolization, the endovascular placement of extender cuffs for type 1 leaks, laparoscopic clipping of side branches for type 2 leaks, and conversion to open repair (33–38). The most commonly used method of endoleak treatment is embolization. This has been extensively reported for the treatment of type 2 leaks. It was first described in 1997 with a technique involving microcatheters tracked through the feeding vessels back to the aneurysm sac (33). Many authors have reported on single-center experiences with both transarterial and translumbar approaches to cannulate the endoleak channel and embolize the feeding vessels (34). Many different materials have been used, including coils, glue, particles, and thrombin, with variable results. Most authors report that type 2 endoleaks classically have inflow and outflow vessels and behave physiologically like an arteriovenous malformation. As a result, the embolization of a single feeding vessel can be ineffective and can make future interventions more difficult (35, 36). We currently advocate the embolization of all feeding vessels visualized during angiography as well as the endoleak itself. This effectively obliterates the “nidus” of the endoleak as well as the feeding vessels treating it as an AVM.

The embolization of type 1 endoleaks is a more controversial subject. The ideal treatment

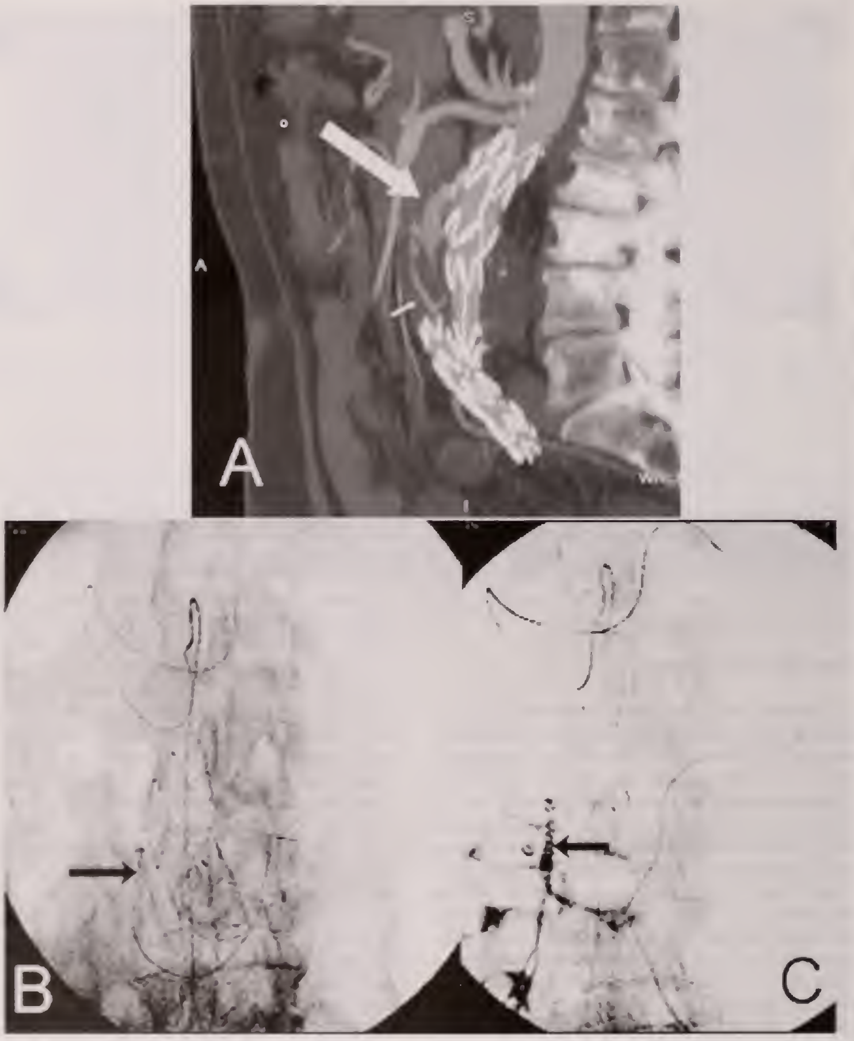

Fig. 10. **(A)** Sagital reformat of a mutidetector CTA of a patient who has undergone endovascular repair of an infrarenal abdominal aortic aneurysm There is an endoleak (large arrow) anterior to the stent-graft. The leak is in continuity with the inferior mesenteric artery (small arrow), suggestive of a type 2 leak. **(B)** Angiography after selective catheterization of the inferior mesenteric artery (arrow) from the superior mesenteric artery via the arc of Riolan. **(C)** Following embolization of the inferior mesenteric artery at its origin (arrow) off the aneurysm, there is no inflow to the endoleak.

for type 1 endoleaks is usually the placement of proximal or distal extender cuffs to tighten the seal and obliterate the endoleak channel. With the recent development of transrenal devices, this option has been replaced for the treatment of proximal type 1 leaks. Our center has had extensive experience with embolization of type I leaks and has found it to be an effective treatment option (39).

Summary

Embolization has recently emerged as a first-line treatment for many vascular lesions that are considered at high risk with surgical repair. The technological advances in microcatheters and new, safer embolic agents have permitted a wider range of applications of this form of treatment. As more experience is gained with these procedures and long-term results are reviewed, this procedure will increasingly gain acceptance as first-line treatment for many more vascular lesions. Endovascular specialists will surely rely more and more on these procedures to assist in the management of all aspects of vascular disease.

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Endovascular Treatment of Neurovascular Disorders

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Abstract

Endovascular therapy is a well-established treatment modality for a variety of cerebrovascular central nervous system disorders. The past few decades have witnessed dramatic improvements in the field of neuroendovascular surgery. These techniques are now used in the treatment of intracranial aneurysms, vascular malformations, carotid stenoses, intracranial vascular stenoses and acute ischemic stroke. In many cases, these techniques provide minimally invasive alternatives to traditional surgery. In addition, neuroendovascular approaches provide treatment options for conditions previously thought to be untreatable. Ongoing device developments and refinements continue to revolutionize the field. These refinements, along with a better understanding of the disease processes, will allow minimally invasive neuroendovascular techniques to be used for a wide spectrum of neurological diseases.

Key Words: Endovascular therapy, intracranial aneurysms, arteriovenous malformations, carotid stenosis, intracranial stenosis, stroke, embolization, thrombolysis.

Introduction

PATIENTS WITH COMPLEX neurovascular disorders often present a great challenge to the neurovascular surgeon. Recent improvements in critical care and microneurosurgery have improved the outlook for many of these patients, who previously had little chance of survival. Despite these advances, the treatment of neurovascular disorders still poses unresolved problems. Endovascular therapy offers a unique potential for providing elegant solutions to neurovascular problems. In addition, it provides minimally invasive alternatives to traditional surgery for the treatment of many vascular and nonvascular central nervous system disorders.

Neuroendovascular surgery is based on remote access to neurovascular structures, and interventions are based on agents delivered within these compartments. These interventions are performed in a superselective fashion, using "image guidance." Several important technical advances in image guidance have emerged during the past few decades. The development of digital subtraction angiography (DSA) and other technological advances in radiography have made possible the development of routinely safe catheterization of high-order vessels. Low-osmolarity, nonionic contrast media have reduced the risk of contrast material reaction. Finally, real-time fluoroscopy, or "road-mapping technique," has been added to DSA to further reduce the toxicity from the burden of the contrast medium.

The development of flexible microcatheters with steerable microwires allows access to high-order bifurcations of the cerebrovascular system. The lumina of these microcatheters allow the use of solid, particulate and liquid embolic agents, such as polyvinyl alcohol (PVA) particles, metallic coils and n-butyl cyanoacrylate (NBCA), at specific sites of abnormality. The ability to access these sites also allows the delivery of therapeutic agents. These agents may be pharmaceutical, catheter bound or implantable, such as tissue plasminogen activator (t-PA), chemotherapeutic agents, angioplasty balloons, stents and platinum microcoils.

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This paper introduces major concepts of neuroendovascular surgery and explains principles involved in the treatment of selected neurovascular disorders.

Endovascular Treatment of Aneurysms

It is estimated that between 1–8% of the population harbors an intracranial aneurysm (1–3). Long-term follow-up of patients with unruptured aneurysms has revealed annual rupture rates of 0.05–3%, with a cumulative rupture rate of 20% at 10 years and 35% at 15 years (4, 5). Subarachnoid hemorrhage (SAH) from intracranial aneurysm rupture continues to be a devastating disease with high morbidity and mortality rates (Fig. 1). Between 40 and 50% of patients with SAH will die because of their hemorrhages (5). The primary purpose of treatment of ruptured aneurysms is to prevent the often-fatal rebleed, allow aggressive treatment of posthemorrhage vasospasm and provide long-term protection against future aneurysmal rupture.

Recent refinements in magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and computed tomography angiography (CTA) have increased the number of unruptured aneurysms detected. Most of these aneurysms will be incidental findings and therefore asymptomatic. If a decision is made to treat these aneurysms, the primary goal of treatment is occlusion of the aneurysm, thereby eliminating the risk of SAH. In addition, since most of these patients are asymptomatic, the morbidity and mortality rates of treatment need to be minimal.

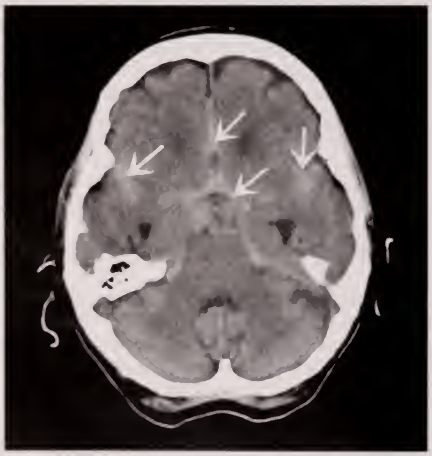

Fig. 1. Axial noncontrast head computed tomography (CT) scan showing extensive subarachnoid hemorrhage. Hyperdensity corresponding to hemorrhage is seen within the basal cisterns, Sylvian fissures and interhemispheric fissure (arrows).

The goal of aneurysm therapy is to prevent rupture by excluding the aneurysm from the vessel lumen. Traditionally, this has been accomplished by surgical clipping of the aneurysm. Embolization that utilizes blood vessels as natural channels to reach the aneurysm via the endovascular route provides a less invasive approach to treatment. Treatment via the endovascular route has the special advantage of avoiding craniotomy, brain retraction, surgical vessel manipulation, possible injury to perforating vessels, and possible postoperative infection or epilepsy. It may also reduce post-treatment hospital stay and recovery time.

An endovascular method using electrically detachable platinum coils has been developed, to provide a less invasive and safer approach to intracranial aneurysms (5–8). The Guglielmi Detachable Coils (GDC) (Target Therapeutics, Fremont, CA) are used to fill the aneurysmal sac, excluding it from the circulation. These coils are very soft, minimizing the trauma on the aneurysmal wall, allowing for maximum packing of aneurysm sac with a low risk of inducing rupture. Since their first clinical use in the early 1990s, GDCs have been utilized in many neuroendovascular centers. To date, more than 80,000 patients have been treated via endovascular embolization (9).

A GDC consists of a platinum coil soldered to a stainless steel delivery wire. The platinum portion is delivered to and detached within an aneurysm. This results in thrombosis and subsequent fibrosis within the aneurysm, excluding it from the circulation. The coil is radiopaque and can be clearly distinguished from the much less opaque delivery wire.

The technique involves several steps. A diagnostic angiogram is performed through the guiding catheter in order to obtain the best view of the aneurysm neck, well separated from the parent vessels. This will determine the "working projection" and the "coilability" of the aneurysm. Aneurysms with high dome-to-neck ratios, without incorporation of the parent vessels, are the most suitable for treatment. However, new techniques, described below, are permitting treatment of wider-necked aneurysms.

An intravenous bolus of 3000–5000 U of heparin is administered prior to proceeding with embolization. This is followed by the administration of 1000 U/hr of intravenous heparin (5000 U/L) in the flushing solution.

Road-mapping is performed, to obtain safe catheterization of the aneurysm with a microcatheter and to deliver the first coil, avoiding any compromise of the parent vessel. Subsequent coils are then deposited using either road-mapping or fluoroscopy, and using the first coil as the landmark delineating the border between the aneurysm and the parent artery. When dense aneurysm packing is achieved, the procedure is terminated and the microcatheter is slowly removed from the aneurysm. A final post-treatment angiogram is obtained to assess the degree of aneurysm occlusion and the configuration and patency of the distal vascular tree (Figs. 2 and 3). Heparinization is reversed with protamine sulfate. In wide-necked aneurysms and in cases where there is some parent vessel impingement, the heparinization is not reversed and aspirin is administered, to reduce the risk of distal embolization.

Since the risk of bleeding from incidental aneurysm is low, elective therapy must have a low complication rate to be warranted. Recent studies of endovascular aneurysm therapy have shown morbidity of 4–4.8% and mortality of 0–1% (10, 11). This compares favorably with the complication rate of microsurgical therapy, for which morbidity and mortality rates of 10.9–17.5% and 2.6–3.9% respectively have been reported in recent meta-analyses (4, 12). Complications encountered during aneurysm coil embolization include thromboembolic event, aneurysm perforation, inadvertent parent vessel occlusion and death (13).

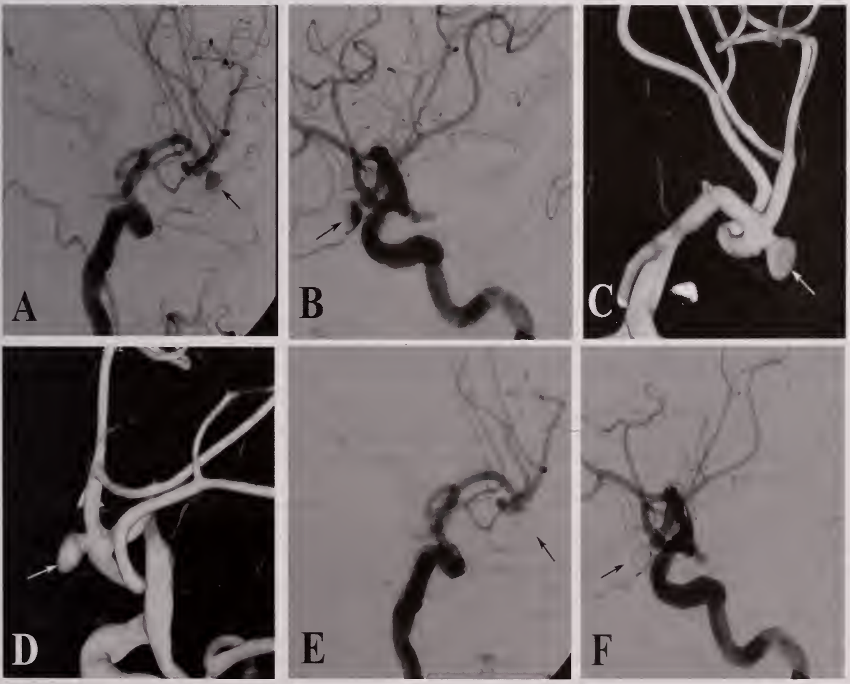

Fig. 2. An angiography of a 68-year-old woman with an incidental middle cerebral artery aneurysm on magnetic resonance maging (MRI). Left internal carotid artery angiograms, **(A)** AP oblique and **(B)** lateral oblique, show a middle cerebral neurysm (arrows) with a small neck. Corresponding 3D rotational angiography images **(C and D)** also show the aneurysm arrows) and its relationship to the normal vessels. Post-embolization angiograms **(E and F)** show occlusion of the neurysm (arrows) and patency of the normal vessels.

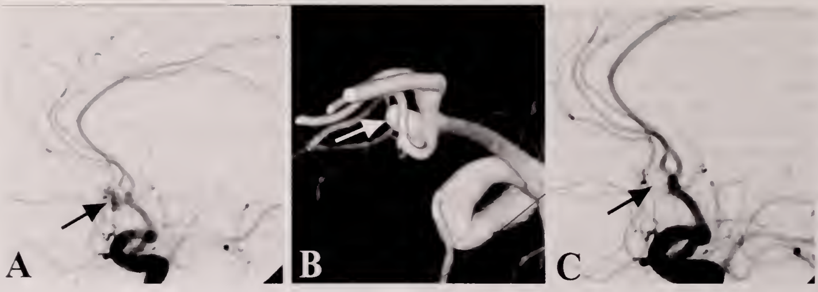

Fig. 3. An angiography of a 48-year-old man who presented with an acute onset of severe headache. Head CT scan showed a subarachnoid hemorrhage. A lateral oblique internal carotid artery angiogram (**A**) reveals a multilobulated anterior communicating artery aneurysm (arrow). The 3D rotational angiography image (**B**) shows the aneurysm (arrow) and its relationship to the normal vessels. Post-embolization lateral oblique angiogram (**C**) shows occlusion of the aneurysm (arrow) and patency of the normal vessels.

The long-term results of GDC coiling compare favorably with surgery in regard to clinical, neuropsychological and radiological outcomes (14). Patients who have undergone aneurysm coiling show less impairment during neuropsychological testing of verbal memory, flexible thinking, ability to resist interference and motor control. Additionally, they do not demonstrate the defects in executive function and memory seen with patients who have undergone aneurysm clipping (15).

The rates of delayed rebleeding after embolization have also been shown to be low. Between 2 and 4% of patients will experience rebleeding after endovascular therapy (16). Yearly rates of 0.4, 0.6 and 2.4% have been reported for years 1, 2 and 3 after therapy, with these rates dropping to 0 in the following three years (17). Rebleeding has also been shown to occur after aneurysm clipping in up to 2.7% of cases over 10 years (18). The best long-term results have been achieved with complete aneurysm occlusion. Therefore, selection of aneurysms with appropriate anatomy for endovascular occlusion will improve immediate and long-term results. The best results have been obtained with the endovascular occlusion of small aneurysms with small necks, while complete occlusion of wide-necked, large or giant aneurysms has been more difficult.

New techniques developed to treat wide-necked, large or giant aneurysms have led to better occlusion rates (19, 20). Balloon inflation across the neck of a wide-necked aneurysm allows dense packing of the aneurysm sac while protecting the parent vessel (21). A nondetachable balloon is advanced to the aneurysm neck before the microcatheter is placed within the aneurysm. Once the microcatheter is positioned within the dome, the balloon is inflated, isolating the vessel lumen. The first coil is positioned, after which the balloon is deflated to assess for motion of the coil. If the coil is stable, it is detached. Subsequent coils are then placed using the same technique until complete occlusion of the aneurysm is obtained.

Improved coil packing can also be achieved by initially bridging the aneurysm neck with a stent. The mesh of the stent allows passage of a microcatheter into the aneurysm. This microcatheter is used to completely occlude the aneurysm with GDC coils (22). The stent allows coils to be retained within the aneurysm and complete aneurysm packing without coil herniation into the parent vessel (Fig. 4). Recently, very small and flexible self-expandable stents have been FDA approved for use in the treatment of wide-necked aneurysms with coils.

Intravascular Embolization of Brain Arteriovenous Malformations

An arteriovenous malformation (AVM) consists of a nidus of coiled and tortuous vascular channels shunting blood from arterial feeders to draining veins. Successful treatment of brain AVMs requires a multidisciplinary approach. The neuroimaging, anatomical, functional, and dynamic information regarding a patient with a brain AVM needs to be reviewed by vascular neurosurgeons, interventional neuroradiologists, and radiosurgeons. The team then needs

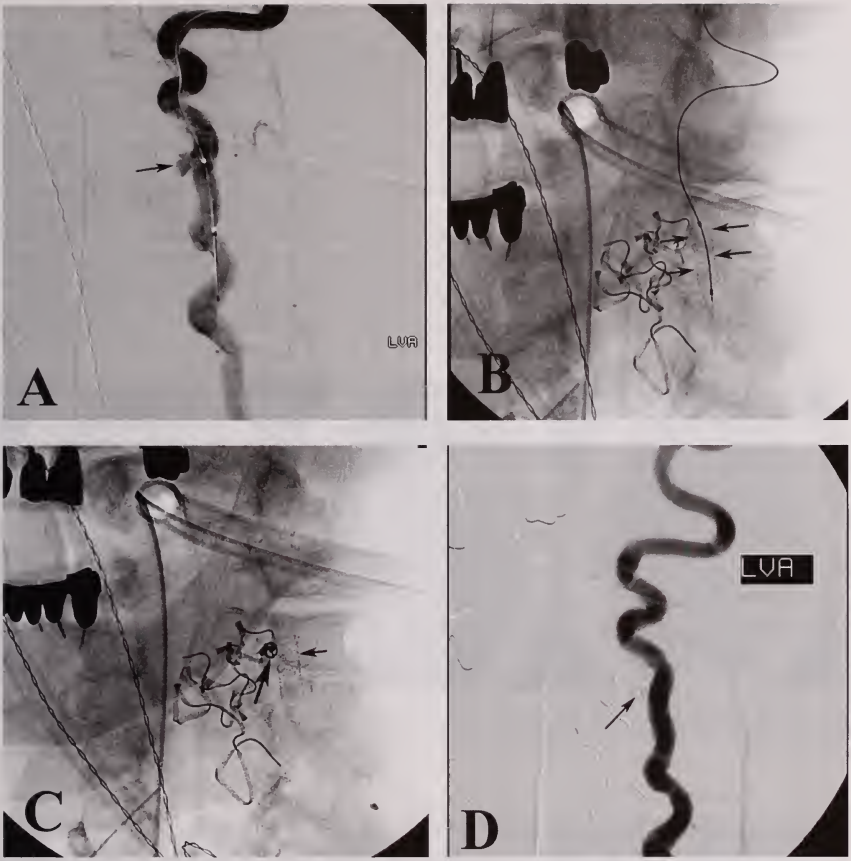

Fig. 4. An angiography of a 62-year-old woman who presented with an iatrogenic injury to the left vertebral artery (VA). Left VA angiogram **(A)** shows a traumatic pseudoaneurysm (arrow) at the level of C3. **(B)** A stent was placed across the origin of the aneurysm (arrows). **(C)** Embolization was performed by placing coils (large arrow) into the aneurysm through the stent mesh (small arrow). **(D)** Post-embolization angiogram shows occlusion of the aneurysm (arrow) and patency of the left VA (LVA).

to discuss and formulate a strategic treatment plan, weighing the conservative approach vs. surgery vs. radiosurgery vs. embolization, or some combination of these.

Approximately 53% of patients with this congenital lesion present with intracranial hemorrhage, 30% with seizures and an additional 12% with progressive neurologic deficit (23). The hemorrhage rate is 1.3–3.9% yearly for patients without previous bleeding. The risk of future hemorrhage increases to 33% for patients who have had a previous hemorrhagic episode (24–26). The morbidity of AVM hemorrhage varies from 55–81% (27), while the mortality rate ranges from 10–17% (27–29).

The goal of therapy is complete obliteration of the vascular nidus. Until this is accomplished, the risk of hemorrhage persists (30–32). Endovascular embolization, microsurgery and radiosurgery are used to treat these vascular malformations. Endovascular embolization with liquid adhesive, particles or ethanol is the least successful of these modalities when used in isolation, leading to cure in only 10% of patients (33–36). Embolic therapy, however, is a useful adjunct to microsurgery or radiosurgery. Preoperative embolization reduces the flow into the AVM and potentially decreases the morbidity and mortality associated with surgical therapy (Fig. 5 and 6). In addition, the size of the nidus can be reduced to allow successful radiosurgical therapy, by decreasing the volume of AVM targeted by radiation (37, 38).

The embolization procedure is performed under heparinization, as described in the section on aneurysms. Microcatheterization of the feeding vessels is performed using a combination of flow-directed and wire-directed catheters. Preferentially, flow-directed catheters are used to reduce the risk of wire injury to the delicate vessels supplying the AVM. After catheterization of the feeding vessels, embolization of the feeding artery is performed, with or without embolization of the nidus of the AVM. Our preferred embolic material is n-butyl cyanoacrylate. Its polymerization time, amount, and type of injection are selected, depending upon the information gathered from the angiogram (39). After the embolization procedure is finished, systemic heparinization is reversed with prota-

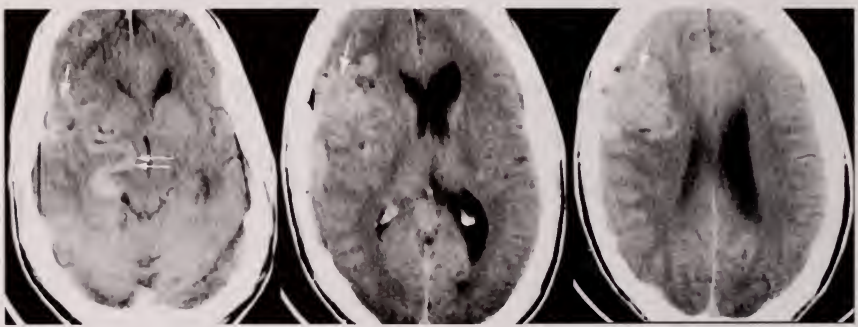

Fig. 5. An angiography of a 40-year-old man who presented with intractable seizures. Axial noncontrast images show a large right frontal arteriovenous malformation (AVM). The nidus (arrow) and draining vein (small double arrow) are seen on the CT scan.

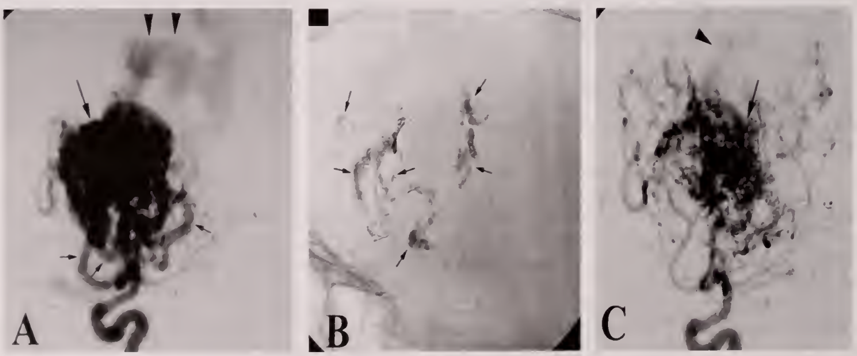

Fig. 6. Angiographic images of the patient described in Fig. 5. Pre-embolization angiogram (**A**) shows the AVM nidus (large arrow), arterial feeders (small arrows) and draining vein (arrowheads). Post-embolization lateral skull x-ray (**B**) shows embolic material from multiple embolization sessions (arrows). Final post-embolization angiogram (**C**) shows decreased filling of the nidus (arrow) and decreased opacification of the draining vein (arrowhead), indicating decreased arteriovenous shunting.

mine, and the patient is taken to the intensive care unit for an overnight stay.

A staged transfemoral embolization is performed in most large or giant AVMs. The time between embolizations can be 3 days to several weeks, depending on the flow dynamics of the AVM and whether there are technical or clinical complications. The waiting period between the last embolization and surgery is 1–4 days. If there is angiographic evidence of untoward occlusion or marked stagnation of the dominant venous drainage of a partially embolized AVM, then surgical resection of the AVM is performed as soon as possible.

Carotid Stenting

Cerebrovascular disease is the leading cause of neurologic disability and the third leading cause of death in the adult population of the United States. Approximately 700,000 people will have strokes this year (40). Approximately 20–30% of these strokes are the result of carotid bifurcation atheromatous disease (41). Carotid stenosis may cause ischemic events by reducing cerebral blood flow or by acting as sources of thromboemboli. Randomized trials have established carotid endarterectomy to be an effective therapy for patients with significant carotid stenosis (42–44). Additionally, carotid endarterectomy (CEA) may reduce the risk of ischemic events and overall mortality for patients with asymptomatic stenosis (44, 45). However, CEA still has significant risks. Depending on the series, the perioperative stroke rate varies from 1.5–9%, while cranial nerve palsies are seen in 7.6–27% of patients undergoing carotid endarterectomy (46, 47).

Carotid stenting (CS) is a less invasive, percutaneous procedure that is being investigated as an alternative to CEA (Fig. 7). CS may allow avoidance of some of the perioperative complications associated with CEA, including wound complications, cranial nerve damage and the risks of general anesthesia (48). In addition, carotid stenting results in significantly less hemodynamic ischemia than endarterectomy, since there is minimal, if any, carotid occlusion time. Initial reports suggest that CS can be performed with a 30-day stroke/death rate comparable to that of CEA (49). Recent studies have shown an acceptable long-term result as well (50, 51). At the present time, carotid stenting may be particularly useful for patients who are poor surgical candidates, have received prior radiation, or have bilateral lesions, restenosis or carotid dissections (Figs. 8 and 9).

Patients are premedicated with dual antiplatelet agents, usually aspirin and clopidogrel. Under local anesthesia, a baseline carotid angiogram is performed and the degree of stenosis is ascertained. The diameters of the stenosis and adjacent segments are measured. The patient is administered 5000 U heparin at the start of the procedure. A 6 French sheath is introduced and advanced from the femoral artery to the common carotid artery. The tip is positioned just proximal to the stenosis. A microcatheter is then advanced over a flexible, angle-tipped guidewire (0.14 inch diameter) through the stenosis. Predilation with an angioplasty balloon is performed if the stenosis is too narrow for the stent to pass prior to the placement of the stent across the stenosis. Balloon angioplasty is then performed within the stent to achieve the appropriate vessel diameter (Figs. 7–9). Final carotid and cerebral angiograms are performed to assess for residual stenosis, vessel compromise, thrombus formation, dissection and distant thromboembolic complications. There has been appropriate concern about the risk of thromboembolic events during carotid angioplasty and stent placement. Several studies have documented the release of emboli during the procedure (52, 53). Newer techniques, including placement of a balloon or filter in the distal internal carotid artery (ICA), have shown promise, with fewer periprocedural ischemic events (52–54).

Intracranial Stenosis

Atherosclerotic disease of the intracranial vessels accounts for approximately 6–29% of ischemic strokes. Despite antithrombotic therapy, many patients have additional ischemic events. In Thijs' study (55), 55.8% of patients who were treated with antithrombotic medicines had ischemic events during the treatment period. Patients with symptomatic stenosis of the posterior circulation have also been shown to have stroke rates of 8–40%, depending on the vessel involved (56–58). Additionally, the results of the External Carotid Internal Carotid Bypass Surgery Group have been similar to those of aspirin therapy alone (59). The poor prognosis with medical and surgical therapy has led to the search for alternative therapies.

The successful treatment of cervical carotid artery stenosis has led to the treatment of intracranial stenosis with angioplasty and/or

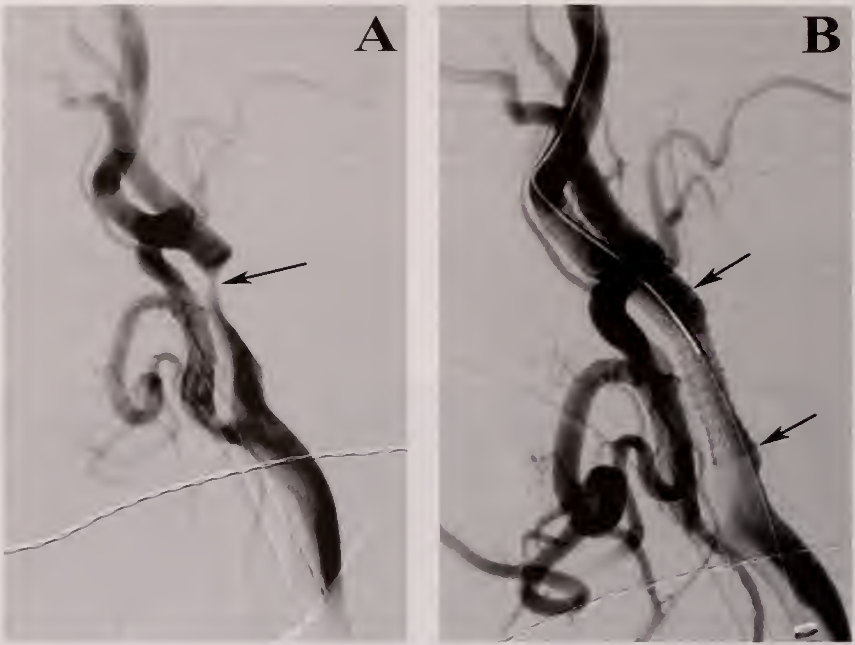

Fig. 7. A 74-year-old man with a history of a right hemispheric stroke. Lateral right common carotid angiogram (**A**) demonstrates 95% stenosis (arrow) of the internal carotid artery. He was referred for angioplasty and stenting because of co-morbid disease. Angiogram after angioplasty and stenting (**B**) shows extent of stent (arrows) and no significant residual stenosis.

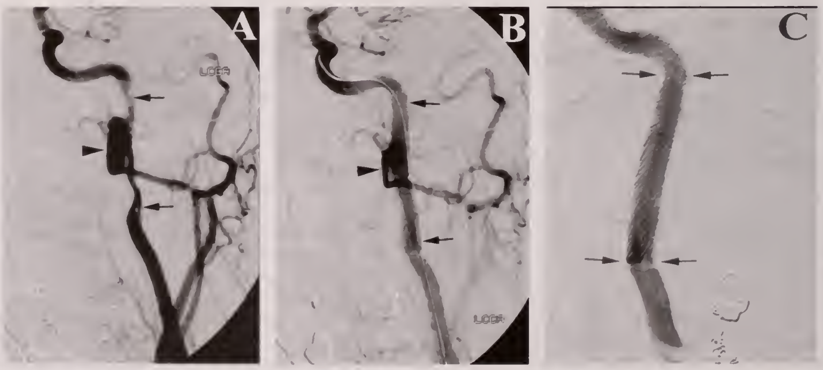

Fig. 8. A 41-year-old man who presented after a rollerblading fall with severe back and neck pain. Left common carotid artery angiogram (**A**) shows carotid stenosis (arrows) and a traumatic aneurysm (arrowhead), indicating carotid dissection. Post-stenting angiogram (**B**) shows no residual stenosis across the stent (arrows) and slight decrease in filling of the aneurysm (arrowhead). Six-month follow-up angiogram (**C**) shows no residual or recurrent stenosis across the stent (arrows) and complete occlusion of the aneurysm.

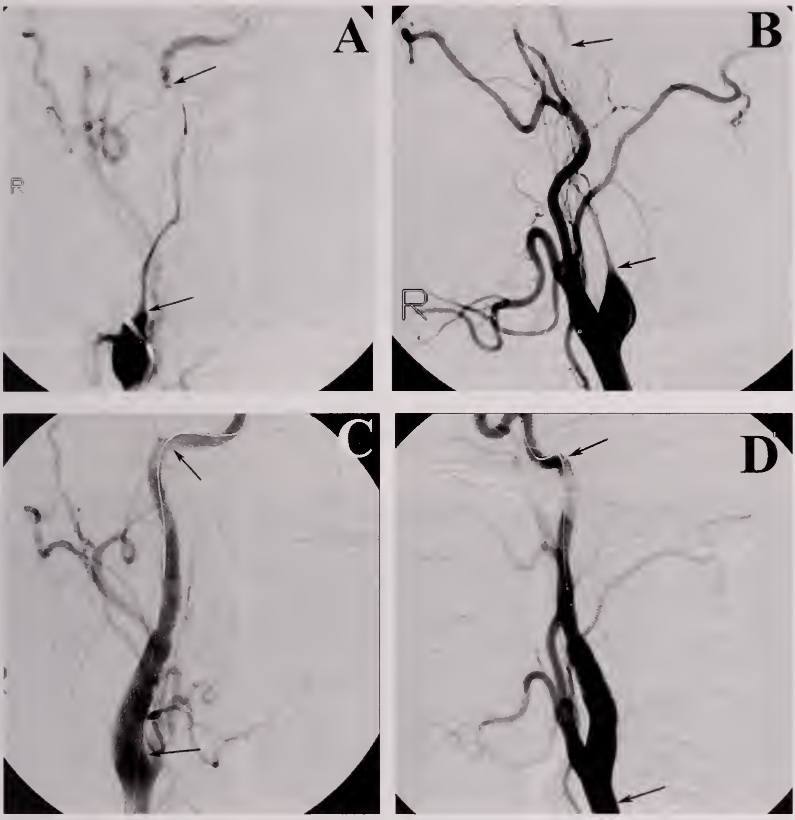

Fig. 9. A 40-year-old man who presented with left arm weakness and neck pain. Head CT scan showed a small infarct in the right putamen. Carotid duplex showed right carotid dissection and stenosis. AP **(A)** and lateral **(B)** right common carotid artery angiograms show dissection extending from the carotid bulb to the petrous segment (arrows). Angiograms **(C and D)** after the placement of three telescoping stents (arrows) show reopening of the internal carotid artery with no significant residual stenosis.

stenting (Figs. 10 and 11). Studies have shown technical success rates of 91–94% in reducing the degree of vessel stenosis (60, 61). However, compared with extracranial vessels, angioplasty of intracranial vessels has a higher complication rate, with strokes occurring in 12–33% of cases (62–64). These complications are attributed to vessel dissection, small vessel occlusion or thromboembolism.

The placement of intravascular stents has been shown to reduce the complications of angioplasty by excluding the atherosclerotic plaque and regions of dissection from the vessel lumen. Additionally, stent placement lowers the degree of residual stenosis and the rate of restenosis by reducing vessel elastic recoil (Figs. 10 and 11). Intracranial stent use has previously been limited because of difficulties in navigating small, tortuous vessels. However, with advances in catheter and stent technology, intracranial, stent-assisted angioplasty is becoming a viable alternative (60).

Stroke Therapy

The majority of ischemic strokes are due to thromboembolic arterial occlusion (65), with

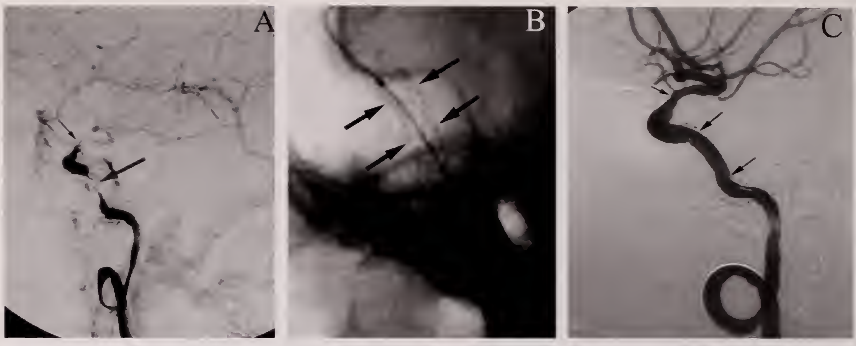

Fig. 10. A 69-year-old man with left hemispheric transient ischemic attacks (TIAs) was found on angiography (**A**) to have severe stenosis of the left internal carotid artery (ICA) at the petrous-cavernous junction (large arrow). Note the poor filling of the distal left ICA (small arrow). (**B**) A stent (arrows) was placed across the stenosis. (**C**) Post-stenting angiogram shows no residual stenosis across the stent (large arrows) and improved filling of the distal ICA (small arrow).

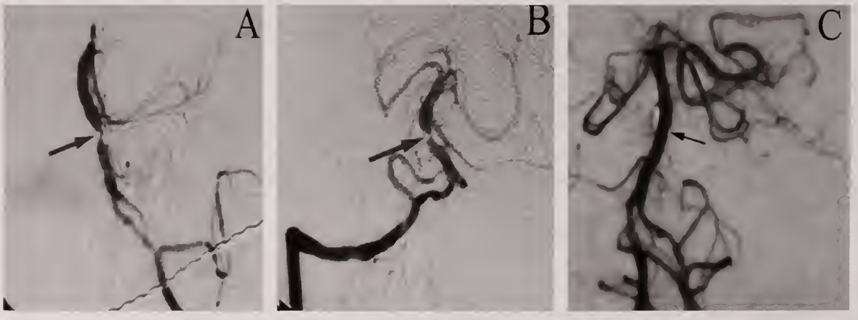

Fig. 11. A 68-year-old man with history of dizziness and inability to stand for prolonged periods of time without becoming symptomatic. Lateral (**A**) and AP (**B**) right vertebral artery angiograms show severe stenosis of the mid-basilar artery (arrows). Angiogram after angioplasty and stenting (**C**) shows no significant residual stenosis (arrow).

75% occurring in the ICA distribution (66). While mortality from middle cerebral artery strokes is low, there is a high morbidity, with only 20–25% of patients returning to an independent lifestyle. Posterior circulation strokes are more ominous, with significant mortality rates, up to 86.4% in one study (67).

Over the past few years, there has been intensive investigation of intravenous thrombolytic therapy for the treatment of acute ischemic stroke. At the present time, only tissue plasminogen activator (t-PA), when administered within three hours of symptom onset, has definitively been shown to be an effective therapy. The benefits of this therapy were demonstrated in the National Institutes of Neurologic Disorders and Stroke (NINDS) sponsored trial in 1995 (68). This trial led to the FDA approval of t-PA for stroke treatment in June 1996. At present, only a small fraction of potentially eligible stroke patients are receiving treatment. The primary reason that patients are not eligible for this treatment is the very short, three-hour time window from symptom onset in which the agent should be administered. Intra-arterial recombinant t-PA (rt-PA) is suggested to be more effective than intravenous rt-PA. In local intra-arterial (IA) thrombolysis, fibrinolytic agents are infused distal to, proximal to, and directly within thrombotic occlusions of mainstem cerebral arteries, using an endovascular microcatheter delivery system (Fig. 12). Direct infusion of thrombolytic agent near the thrombus allows greater concentration of agent, fewer systemic effects, more rapid dissolution of large or multiple clots, and an opportunity to carry out gentle mechanical disruption of the clot with the delivery catheter and wire (69). IA thrombolysis also has a number of potential disadvantages, including manipulation of a catheter within cerebral vessels, potentially increasing vulnerability to hemorrhage; the requirements for systemic heparinization during catheterization to deter catheter-induced thrombosis; and delay in initiation of thrombolysis. The procedure is labor and capital intensive, and the number of facilities skilled in IA thrombolysis is small.

Intra-arterial thrombolysis may be used in the anterior circulation (carotid circulation) up to 6 hours after onset of symptoms, although better results have been shown when administered within 3 hours (70). It is also used up to 12–24 hours after onset in posterior (vertebrobasilar) circulation lesions, because of the poor prognosis without therapy (67). Despite the increased rate of symptomatic hemorrhage with intra-arterial administration of rt-PA, many trials have still demonstrated improved clinical outcomes versus placebo.

Of particular note is the first Phase III trial of IA thrombolysis, the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial (69). In PROACT II, patients within 6 hours of symptom onset with symptomatic M1 or M2 middle cerebral artery (MCA) occlusions were randomized to receive IA thrombolysis with systemic heparinization vs. heparinization alone. The prespecified primary outcome in PROACT II, a good or excellent score on the modified Rankin Scale of handicap, was achieved by 40% of the IA group vs. 25% of control patients ($p=0.043$). In addition, recanalization rates 2 hours after initiation of infusion were markedly increased in the IA group. Intracerebral hemorrhage rates at 36 hours were increased in the IA group; however, no difference in overall mortality between the two groups was observed.

Another potential role for intra-arterial rt-PA is for postoperative stroke patients. The risk of stroke is approximately 2.9% in the immediate postoperative period (71). During a recent multicenter study of intra-arterial rt-PA administered during the immediate postoperative period, good results were obtained with only minimal complications. The local delivery of thrombolytic agent reduces systemic effects. Only patients who had previously undergone intracranial surgery had an unacceptably high complication rate (71).

Further research is being conducted in the use of mechanical thrombolytic devices, as well as laser clot fragmentation (72). The advantages of these approaches include lack of systemic and hemorrhagic complications. Better public awareness is also needed, since fewer than 5% of eligible stroke patients actually receive thrombolytic therapy (73). In addition, faster

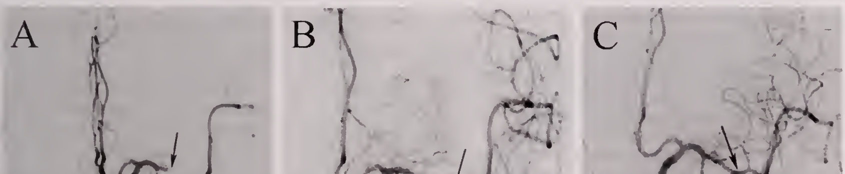

Fig. 12. A 65-year-old woman who presented 3.5 hours after the onset of right-sided weakness and aphasia. Head CT scan did not show a hemorrhage or definite infarct. An emergency angiogram (**A**) showed a left internal carotid artery (ICA) occlusion of the superior M2 branch of the middle cerebral artery (MCA) (arrow). Intra-arterial infusion of t-PA was begun distal to, within and proximal to the site of occlusion. Angiogram after infusion of 6 mg t-PA (**B**) shows partial reopening of the M2 branch and residual thrombus within the branch (arrow). Final angiogram (**C**) after infusion of 13 mg t-PA (C) shows reopening of the previously occluded M2 branch (arrow).

diagnosis with MR diffusion and CT perfusion may help to identify patients who can benefit from thrombolysis.

Conclusions

Neuroendovascular techniques provide innovative solutions for many neurovascular disorders, including minimally invasive treatment options for many patients with complex neurovascular disorders. These techniques may allow for the treatment of previously "untreatable" disorders.

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Minimally Invasive Vein Surgery

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Abstract

Advances in minimally invasive vein surgery (MIVS) techniques made during the last decade have decreased operative morbidity, the number and size of incisions, operative time and recovery time. The following MIVS techniques will be discussed:

1. Transilluminated Powered Phlebectomy (TIPP) TriVex™
2. Radiofrequency Ablation Greater Saphenous Vein (RFGSV) Closure®
3. Laser Ablation Greater Saphenous Vein (EVLT)
4. Subfascial Endoscopic Perforator Surgery (SEPS)
5. Percutaneous Vein Valve Bioprosthesis (PVVB)

The techniques used in MIVS allow surgeons to manage venous pathophysiology associated with all three venous systems of the lower extremities. The results are comparable to those obtained with open procedures.

Introduction

MINIMALLY INVASIVE TECHNIQUES for vein surgery have evolved over the last decade, revolutionizing the management of venous disease.

Endoscopic, endovascular and mechanical methods have supplanted longstanding traditional procedures and allow surgeons to manage the venous pathophysiology associated with all three (superficial, perforator and deep) venous systems in the lower extremities (1). These techniques decrease operative morbidity, the number and size of incisions, operative time, and recovery time. In addition, the results are as durable as the open procedures, or more so, with increased patient satisfaction and effective wound healing rates in applicable instances.

MIVS techniques include:

1. Transilluminated Powered Phlebectomy (TIPP) (TriVex™ , Smith and Nephew, Inc., Andover, MA)
2. Radio-frequency Ablation Greater Saphenous Vein (RFGSV) Closure® (VNUS Medical, San Jose, CA)
3. Laser Ablation Greater Saphenous Vein (EVLT)
4. Subfascial Endoscopic Perforator Surgery (SEPS)
5. Percutaneous Vein Valve Bioprosthesis (PVVB)

Each of these techniques is discussed, to provide an overview of corrective procedures available in the era of minimally invasive vein surgery (MIVS).

Discussion

Transilluminated Powered Phlebectomy, TriVex™

Transilluminated Powered Phlebectomy (TIPP) is a mechanical method of ablating

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Dr. Elias has disclosed that he serves as consultant to Smith and Nephew, Inc., Andover, MA and US Surgical, Norwalk, CT and is preceptor to VNUS Medical, San Jose, CA and Diomed, Inc., Andover, MA.

branch varicosities. Traditional excision of branch varicosities utilizes either hook phlebectomy or stab avulsion, which typically involves multiple incisions (as many as 25–30) and an average operative time of 1–3 hours. TIPP, brand name TriVex™ (Transilluminated Varicose Vein Extraction), involves an average of 3.5 incisions and an operative time of 16–20 minutes (2). The TIPP technique, first developed by Chesire et al. (3), utilizes two devices, the transilluminator/irrigator and the powered resector (Fig. 1).

The transilluminator/irrigator allows the surgeon to visualize the varicosities and infuse 1st and 2nd stage tumescent anesthesia before and after resection, which aids in partial exsanguination of the veins, hemostasis, and pain relief (Fig. 2). The resector is placed immediately under or next to the varicosities in the subcutaneous tissue. The veins are then suctioned into the rotating blade, where they are cut into small pieces and removed (Fig. 3). Successful vein removal can be documented by transillumination.

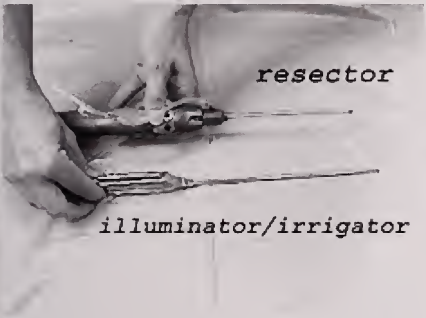

Fig. 1. TriVex™ transilluminator/irrigator and powered resector. Courtesy of Smith & Nephew, Endoscopy, Andover, MA.

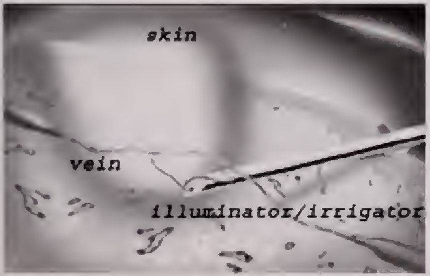

Fig. 2. Tumescent anesthesia causes hydrodissection, which aids in removal of the varicosities. Courtesy of Smith & Nephew, Endoscopy, Andover, MA.

This technique has been utilized since early 2000, when the initial clinical trials were completed (3). Advantages of this minimally invasive surgical technique are short operative time, minimal number of incisions, accurate removal of varicosities due to better visualization, and patient satisfaction comparable to satisfaction from traditional methods. Technical complications are associated with inexperience and tend to occur early on in the learning curve. They consist primarily of bruising, hematoma formation and fat necrosis. These complications are similar to adverse events associated with traditional excision and are minimized with experience (4).

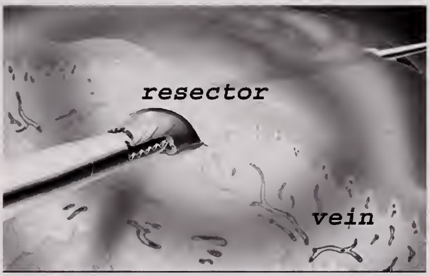

Fig. 3. TriVex™ System Resector morcellating vein. Courtesy of Smith & Nephew, Endoscopy, Andover, MA.

Radiofrequency Ablation (Closure®) and Laser Ablation (EVLT) Greater Saphenous Vein

Radiofrequency (Fig. 4) and laser ablation (Fig. 5) are endovascular approaches to saphenous vein incompetence. Traditional stripping and removal of the saphenous vein requires incision sites at the groin and knee or ankle level. The open procedure requires either general or regional anesthesia. Morbidity from traditional stripping may include hematoma, pain and saphenous neuropathy.

Endovenous ablation of the saphenous vein is performed by obtaining percutaneous access to the greater saphenous vein, most commonly at the level of the knee under duplex ultrasound guidance. A guidewire is then advanced to the saphenofemoral junction, over which the Closure® or EVLT catheter is passed (Figs. 4 and

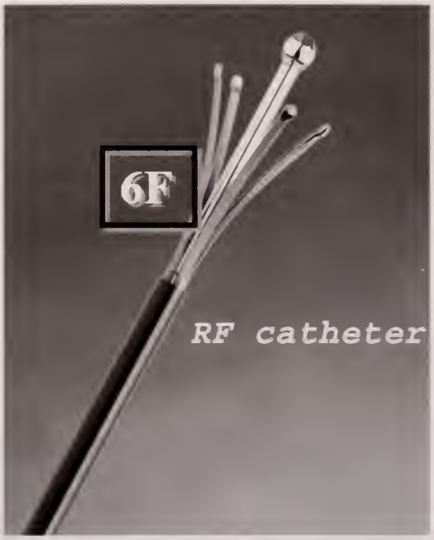

Fig 4. Radiofrequency catheter. Courtesy of VNUS Medical, Sunnyvale, CA. 6F refers to diameter of catheter.

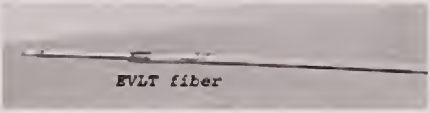

Fig. 5. Laser (EVLT) fiber.

5). The radiofrequency or laser energy is transmitted to the vein wall, causing it to contract and close. Endovenous ablation of the saphenous vein is performed using local anesthesia and sedation. No incisions are necessary, and the patient can return to normal activity the following day. Radio-frequency technology and laser ablation have been utilized for the past 5 years and 3 years respectively. More than 90% of saphenous veins remain closed two years after the procedure. These results compare favorably with traditional procedures, with decreased morbidity and increased patient satisfaction (Fig. 6) (5, 6).

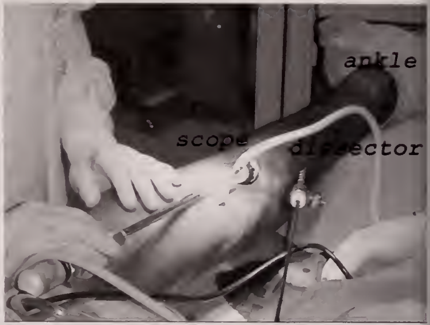

Fig. 6. Remote incision sites for endoscope and working port incision for dissection and perforator clipping.

Subfascial Endoscopic Perforator Surgery

Perforator incompetence is prevalent in patients with venous stasis ulceration (more than 90% of patients have the condition) (7). Under normal conditions, blood flows from the superficial system to the deep venous system via the perforator veins. Incompetent perforator veins cause venous pressure to be reversely directed toward the skin, resulting in venous hypertension and stasis ulceration.

Traditional methods of open perforator ligation (Linton's procedure) require incision to be made through edematous, infected fields within the ulcer bed. Wound dehiscence and significant postoperative pain are reported in 20–40% of patients (8). Hospital admission is usually necessary.

Subfascial Endoscopic Perforator Surgery (SEPS) is an operative technique with an endoscopic approach to incompetent perforator vein ligation. Incisions are made remote from the site of ulceration (Fig. 6), and balloon dissection is utilized to create a subfascial space using CO_2 insufflation similar to laparoscopy (Fig. 7). These two factors minimize both wound complications (by placing incision sites in healthy skin) and complaints of postoperative pain (by utilizing blunt balloon dissection). A 10 mm incision is used for placement of the endoscope and a 5 mm working port incision for dissection and perforator clipping (Fig. 8). After placing the clips, the pressure in the veins is reduced, so that healing of any ulceration is enhanced.

Postoperative pain is minimal and patients are able to continue wound care the following day. Stasis ulcer healing rates and maintenance of healing 5 years after SEPS range from 90% for patients with a normally functioning deep venous system to 75–80% for patients with deep venous insufficiency, when combined with compression therapy and wound care (9, 10). Aver-

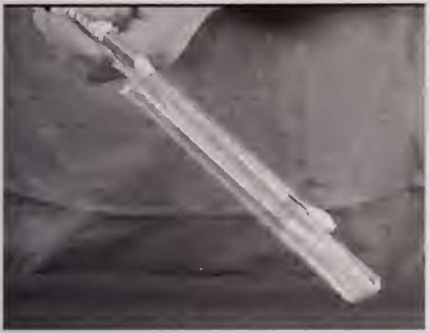

Fig. 7. Balloon dissector.

age healing time for ulceration is six weeks. As with the other minimally invasive techniques, SEPS allows direct visualization of venous pathology with significantly lower morbidity.

Percutaneous Vein Valve Bioprosthesis

A significant number of patients with venous stasis ulceration have associated deep venous insufficiency (11, 12). To date, surgeons have been hesitant to repair and improve deep venous flow hemodynamics; however, a few centers do aggressively treat deep venous incompetence. Traditional surgical methods include axillary vein valve transplant, valvuloplasty, and vein valve transposition (13). All of these methods require significant incisions and in-house recovery time.

Percutaneous Vein Valve Bioprosthesis (PVVB) is a technique used to correct valvular incompetence by utilizing a percutaneous approach to deliver a functioning vein valve to an incompetent segment of the deep venous system. The device consists of a glutaraldehyde-treated bovine jugular vein with a competent valve mounted on a nitinol stent (Fig. 9). Percutaneous access is obtained at the level of the internal jugular vein. A guidewire and introducer are advanced to the level of the femoral vein (old nomenclature, "superficial femoral"). The bovine valve is then passed along the introducer to the femoral vein at the site of valvular incompetence and deployed (Fig. 10). The technique is similar to a placement of a vena cava filter.

This procedure is now in phase 1 clinical trials to evaluate safety and efficacy. The potential benefits of this minimally invasive approach include: small remote incision, same-

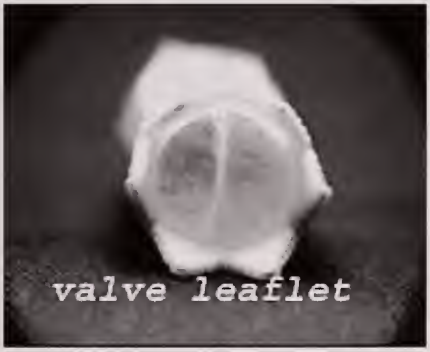

Fig. 9. Bovine jugular vein mounted on nitinol stent. Courtesy of VenPro, Irvine, CA.

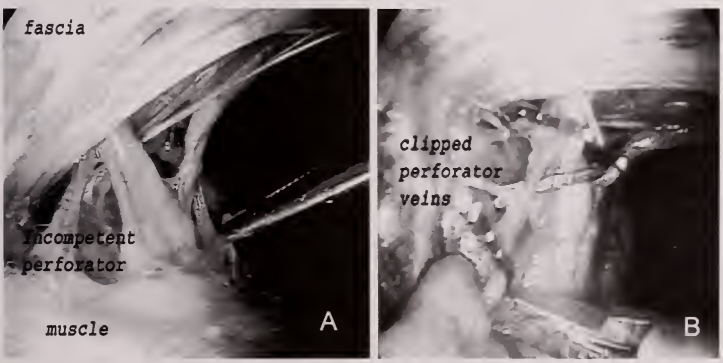

Fig. 8. (A) Endoscopic view of perforator vein prior to clipping. (B) After clipping.

day surgery, local anesthesia, and perhaps the ability to place multiple valves to mimic a normally functioning deep venous system.

Conclusion

The advent of minimally invasive vein surgery techniques allows the surgeon to manage venous pathophysiology associated with all three venous systems in the lower extremities. Many patients may require a combination of MIVS techniques to correct venous insufficiency and stasis changes. These techniques complement each other, and when combined, can enhance the clinical outcome. MIVS can be performed as an outpatient procedure with few, if any, small incisions. MIVS techniques, which incorporate endoscopy, transillumination, ultrasound or fluoroscopy, also make it possible for the surgeon to visualize venous pathology. From the vascular surgeon's perspective, it is reassuring to "see" the pathology. In addition, patient satisfaction is enhanced by minimal discomfort and less postoperative morbidity as compared to traditional open procedures.

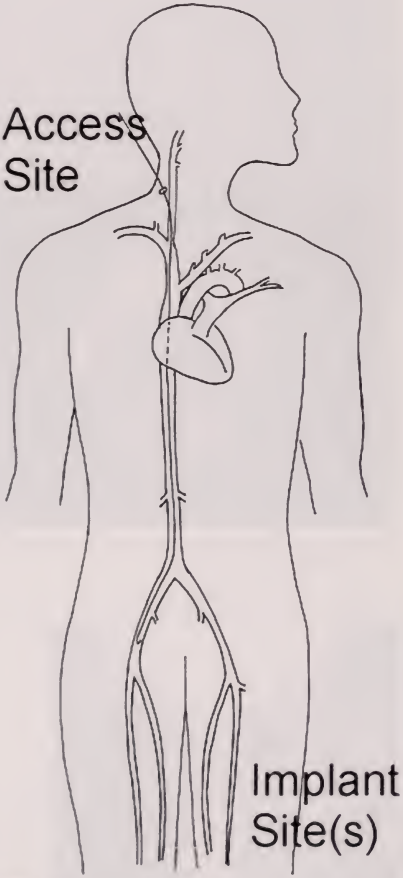

Fig. 10. Percutaneous access site and vein valve implant site(s). Courtesy of VenPro, Irvine, CA.

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A Review of Heart Failure Treatment

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Abstract

Heart failure is a common and costly medical condition. Ischemic heart disease and hypertension account for most cases of heart failure in developed countries. Estimates of the one-year mortality rates for patients with New York Heart Association (NYHA) Class II, III, and IV are 10%, 20%, and 40%, respectively. Angiotensin-converting enzyme (ACE) inhibitors reduce mortality of heart failure patients by approximately 25% (odds ratio 0.77, 95% CI 0.67–0.88). Larger doses of ACE inhibitors are more effective in preventing hospitalization than are lower doses. Angiotensin II receptor blockers (ARBs) are an alternative for patients who cannot tolerate ACE inhibitors because of their side effects (e.g., cough). Evidence for benefits of using combination of ACE inhibitors and ARBs is encouraging, but requires further study. For patients who cannot tolerate either ACE inhibitors or ARBs, vasodilator therapy with hydralazine and nitrates will probably provide benefit. (Diuretic therapy, while a mainstay of heart failure treatment, is primarily used for symptom relief.) There is also evidence that spironolactone reduces mortality (relative risk reduction 30%, 95% CI 18–40%) for patients with NYHA class III and IV heart failure. When administering spironolactone to heart failure patients, monitoring for hyperkalemia is essential. After two centuries of use, randomized controlled trials have finally demonstrated that digoxin is effective in preventing hospitalizations (relative risk reduction 28%, 95% CI 21–34%). There is now overwhelming evidence that beta-blockers are safe for heart failure patients but that they reduce the risk of death for these patients by approximately 30%. In addition to these medical interventions, heart failure patients may also benefit from a number of non-pharmacological interventions.

Key Words: Heart failure, digitalis, beta-blockers, anti-arrhythmic agents, anticoagulation, ventricular assist device, exercise, randomized controlled trials.

Following the tenets of evidence-based medicine (1), this paper will highlight results from randomized trials and insights from controlled trial methodology which guide us in managing patients with heart failure.

Epidemiology, Diagnosis, and Prognosis

Studies of heart failure incidence suffer from lack of agreement regarding definition, from variability in methods and criteria, and from a paucity of population-based studies. Estimates of heart failure incidence vary from 1.0–5.0 per thousand per annum, increasing substantially with age to a level as high as 40 cases per thousand in those older than 75 years of age (2). This corresponds to a prevalence of 1% in those 50–59, and 10% in those older than 80 (3). Only about 5% of symptomatic patients have severe heart failure (4).

In the more industrialized countries, ischemic coronary disease and hypertension account for most cases of heart failure (5, 6). Valvular disease and viral, idiopathic and alcoholic cardiomyopathy do occur with somewhat lesser frequency. On occasion, clinicians may see thyroid disease and hemochromatosis, which are treatable causes of heart failure. All told, multiple hospitalizations, the many medications, and the home care requirements result in a yearly cost of treating heart failure patients that may be as high as $22,000 per person (7).

The classic heart failure symptoms of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea lack specificity — many patients with other conditions report identical symptoms (8). The same is true for the most easily detected

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physical sign, peripheral edema (5). This probably explains the findings of two studies that examined the accuracy of the diagnosis of heart failure by primary care physicians and found false positive rates of 47% (9) and 55% (10). Physical findings of a third heart sound, elevated jugular veins, and pulmonary crackles are more specific (11), though the last of these is prominent in one easily confused condition, pulmonary fibrosis. The diagnosis may be more difficult for older patients, of whom 30–40% with heart failure may have primarily diastolic dysfunction (11). The chest radiograph is helpful, despite the poor relationship between heart size and left ventricular function and between upper-lobe distension and pulmonary capillary wedge pressure (12). The limitations of history, physical examination, and chest radiographs lead experts to recommend routine echocardiography for patients suspected to have heart failure. B-natriuretic peptide shows promise as a laboratory test for differentiating between patients with and without left ventricular dysfunction, and may obviate the need for echocardiogram for some patients (13).

A clear picture of the prognosis for heart failure is also difficult, because while studies almost invariably classify patients according to the New York Heart Association (NYHA) functional classification, the between-observer agreement in NYHA class is poor (14). In any case, available evidence suggests that neither the incidence nor the prognosis of heart failure has changed dramatically over the last two decades (15). Despite limitations of the studies, one-year survival rates of older patients with severe heart failure are no higher than 60% (16). A recent population-based study found that one-year mortality of patients hospitalized with heart failure was greater than 30%, with even poorer prognosis for older patients with multiple comorbidity (17). Reasonable current estimates would suggest one-year mortalities for NYHA Class II, III and IV patients of 10%, 20% and 40%, respectively.

Management — Where to Look for Best Evidence

We offer our patients treatment for two reasons: to help them live longer and feel better. Uncontrolled observations, or observations from studies of weak design, may provide misleading estimates of treatment efficacy. Ten years ago, we were offering heart failure patients prophylactic anti-arrhythmic agents that we now know led to premature death, while withholding beta blockers that would have helped them live both longer and better. The cardiology community was divided between vociferous advocates of digoxin and equally vociferous opponents. Only rigorously conducted, blinded, randomized controlled trials (RCTs) in which patient follow-up was complete and patients were analyzed in the groups to which they were randomized (18) have opened our eyes to the true benefits and harms of these interventions.

RCTs are inevitably limited by random error, and by the particular patient population and intervention that the investigators choose to study. Meta-analyses that pool results across RCTs provide a powerful tool to help deal with both of these limitations. To avoid bias, meta-analyses must themselves be rigorously conducted. For these systematic reviews, avoiding bias requires eligibility criteria that are both explicit and appropriate (appropriate, in that across the range of pooled patients, interventions, outcomes and methodologies, we expect more or less the same treatment effect), and a comprehensive and reproducible search for relevant studies (19). Furthermore, investigators must evaluate the methodological quality of the original studies; poorly designed studies will yield biased estimates, regardless of the rigor of the meta-analytic methods. Finally, meta-analysts must look carefully to see if study results are similar for different patients, interventions, measurements of outcome, and study methodologies (20). Our summary of the evidence shall, wherever possible, rely on systematic reviews that meet these criteria.

Judging the Magnitude of Treatment Effects

Because they must always trade off benefit and harm, clinicians cannot be satisfied with just knowing whether treatments work. They must attend also to the magnitude of the benefit patients can expect. The relative risk reduction (RRR) provides one way of expressing the extent to which treatments reduce the relative risk (RR) of an adverse outcome (for instance, they may cut the risk by 1/2 or by 1/4). The RRR may, however, be misleading. For patients with a 2% risk of dying, a treatment with an RRR of 50% will reduce the risk to 1%. The situation is very different when the patient's risk of dying is 40%, when the same treatment will cut the risk to 20%. Thus, the first patient experiences an absolute benefit of 1%, and the second of 20%. A compelling way to present such results uses the number needed to treat (NNT), the number of patients we must treat over a particular time period to prevent an adverse outcome such as death, stroke, or myocardial infarction. We would need to treat 100 of the low-risk patients described to save one life, but only 5 of the high-risk patients (21).

Vasodilators

A rigorously conducted, systematic review of RCTs has examined the effect of angiotensin-converting enzyme (ACE) inhibitors for heart failure (22). The investigators found that ACE inhibitors reduce mortality by approximately 25% (odds ratio 0.77, 95% CI 0.67–0.88). The effect was consistent across all NYHA functional classes and all ACE inhibitors. This implies that clinicians would need to treat approximately 40 NYHA Class II patients and 10 Class IV patients for a year with ACE inhibitors in order to prolong a single life. Another meta-analysis of five trials that used individual data (23) showed a similar result (odds ratio 0.80, 95% CI 0.74–0.87) and also suggested lower rates of admission for heart failure (OR 0.67, 95% CI 0.61–0.74).

Clinicians can be confident of the applicability of these findings if they prescribe the relatively large daily doses of ACE inhibitors used in the RCTs (captopril 100–150 mg, enalapril 20 mg) (24). One large RCT (25) has compared the use of a very large dose of lisinopril to a very small dose, for patients with heart failure. The large dose was associated with a 12% reduction in the RR of death or hospitalization (95% CI 4–18%). These results support administration of high doses of ACE inhibitors for heart failure.

Some patients cannot tolerate ACE inhibitors (ACEIs), most commonly because of cough or renal failure with hyperkalemia. For such patients, what are the options? A systematic review of 17 RCTs of angiotensin II receptor blockers (ARBs) showed a trend toward decreased mortality (OR 0.68, 95% CI 0.38–1.22) and decreased hospitalization (OR 0.67, 95% CI 0.29–1.51) for the relatively small number of patients who participated in placebo-controlled trials of ARBs in comparison with background ACE inhibitor therapy. When compared directly with ACEIs, ARBs showed a weak trend toward increased mortality (OR 1.09, 95% CI 0.92–1.29) and an even weaker trend toward decreased hospitalization (OR 0.95, 95% CI 0.80–1.13) (26). In contrast, the combination therapy of ARBs and ACEIs was superior to ACEIs alone in reducing hospitalization (OR 0.74, 95% CI 0.64–0.86), but not mortality (OR 1.04, 95% CI 0.91–1.20). Subgroup analyses, however, have suggested that patients already on both ACEIs and beta-blockers may do less well when taking an ARB (26).

The combination of hydralazine and an oral nitrate represents another alternative to an ACEI. The evidence supporting this combination comes from a single RCT which reported a mortality rate of 34.3% for 273 placebo-treated heart failure patients and 25.6% for 186 patients treated with hydralazine and nitrates after two years of follow-up (27). The associated RRR of approximately one-third of those patients was on the borderline of conventional levels of statistical significance, and the usually preferable survival analysis failed to cross the conventional 0.05 boundary. A subsequent study demonstrated a mortality reduction when using an ACEI as compared to the hydralazine/nitrate combination (28).

Diuretics

Diuretics are a mainstay of treatment for heart failure patients, and their dramatic impact on symptoms has obviated the necessity for RCTs. Loop diuretics are usually required, though their effectiveness decreases as heart failure severity increases, particularly for patients with decreased renal function, (29, 30). When loop diuretic resistance becomes sufficiently severe, patients require the addition of a thiazide or spironolactone (31). Metolazone is popular in North America, though its continuous use tends to be associated with hyponatremia, hypochloremic alkalosis, and hypokalemia (32). Its best use may be as an intermittent treatment in response to weight gain caused by fluid retention.

A single trial involving 1663 patients with NYHA Class III and IV heart failure has suggested a possible mortality reduction with aldosterone-blocking therapy. Patients received 12.5–50 mg of spironolactone or matched placebo each day, depending on their serum potassium. The study, which was stopped early (mean follow-up of 24 months) because of evidence of benefit, showed an RRR of 30% (95% CI 18–40%). Symptomatic hyperkalemia was infrequent in the context of the trial, but may be more frequent in routine clinical practice.

Digoxin

After two centuries of digoxin use, RCTs have finally yielded a clear picture of the drug's effect on heart failure patients in sinus rhythm. A large Digitalis Investigation Group (DIG) study (33) confirmed the findings of a meta-analysis of small RCTs conducted prior to 1990 (34) and two subsequent RCTs of digoxin withdrawal (35, 36), which suggested that digoxin can reduce the incidence of heart failure exacerbations. After enrolling more than 6,500 patients and achieving an average follow-up of 37 months, the DIG study group found nearly equal mortality among treated and control patients, but a reduction in heart failure hospitalizations with digoxin (26.8% vs. 34.7%, RR 0.72, 95% CI 0.66–0.79).

Previously hospitalized heart failure patients are at high risk of readmission. For instance, consistent with the DIG results, in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial that tested high- and low-dose lisinopril in 3,164 heart failure patients, more than 60% required hospitalization for a cardiovascular cause during an average follow-up of just under 4 years (37). If one were to consider a relatively low yearly risk of hospitalization of 10%, one would need to treat approximately 35 patients with digoxin for a year to prevent one hospitalization. The NNT would drop further for those with a higher hospitalization risk. Digoxin should be administered with caution to patients with renal dysfunction or AV nodal conduction abnormalities.

Beta-Blockers

The literature includes a profusion of meta-analyses of beta-blocker therapy for heart failure (38–43). While methods and results differ, all are sound and yield consistent findings. While increasing the ejection fraction, beta-blockers reduce the relative risk of dying by about 30%, with the lower boundary of the 95% CI of 10–15%. Patients with ischemic and non-ischemic cardiomyopathy can expect similar benefits. For patients with severe heart failure, of whom 40% might die in less than one year, the clinician must treat 8–9 patients with beta-blockers for one year to prolong one life; the number would be around 35 for lower risk NYHA Class II patients. Like digoxin, beta-blockers can exacerbate tendencies to bradycardia or increase the level of AV block in those with AV nodal disease.

One recent meta-analysis suggests the possibility that vasodilating beta-blockers have a larger impact on reducing mortality than do beta-blockers without vasodilating properties (44). However, strong inferences regarding the relative effect of vasodilating and non-vasodilating beta-blockers must await head-to-head comparisons between the two subclasses.

Antiarrhythmic Agents

In the Framingham Heart Study, approximately 50% of all deaths of heart failure patients occurred within one hour of onset of symptoms (45), and sudden death continues to account for half the mortality in recent trials of pharmacologic therapy in heart failure (46).

In the past, cardiologists and internists often responded to Holter monitor findings of nonsustained ventricular tachycardia (NSVT) in patients with coronary artery disease or heart failure by prescribing Class I antiarrhythmic agents that include quinidine, procainamide, disopyramide, mexiletine, encainide, flecainide, and moricizine. Despite the ability of the last three drugs to obliterate nonlethal arrhythmias, individual trials paradoxically have shown that they are associated with a statistically significant increase in sudden death (47, 48). Moreover, a rigorously conducted meta-analysis of all 51 RCTs of Class I agents confirmed an increase in mortality (odds ratio 1.14, 95% CI 1.01–1.28) (49).

In 1997, the investigators of all 13 RCTs of amiodarone, a Class III agent, reported a meta-analysis that combined individual patient data from all of their trials (50). Of these studies, 5 were undertaken for heart failure patients and 8 for patients after myocardial infarction. Their pooled analysis showed an RRR for sudden death of 29% (95% CI 15–41%), and a total mortality of 15% (95% CI 2–29%), with consistent effects in the follow-up trials for myocardial infarction and heart failure. These results suggest that treating 100 NYHA Class II heart failure patients with nonsustained ventricular tachycardia would prolong the lives of 3 patients (NNT approximately 35) and similar treatment for 100 NYHA Class IV patients would prolong 12 lives (NNT approximately 8). However, in treating 100 patients, we would cause 6 patients to become hypothyroid, 1 to become hyperthyroid, 2 to develop bradycardia, and 1 to develop pulmonary infiltrates (49).

Anticoagulation

Most patients with heart failure and atrial fibrillation are likely to choose warfarin therapy to prevent stroke over aspirin therapy or no treatment. A reasonable estimate of the one-year risk of having an embolic stroke for heart failure patients over 65 is 8% (51). A meta-analysis of five RCTs of the use of warfarin for patients with non-valvular atrial fibrillation showed a 68% relative risk reduction, with a CI of 50–79%. With conscientious monitoring of international normalized ratio (INR), the risk of serious gastrointestinal bleeding in the course of one year is likely to be 1% or less (52). Thus, for 100 patients treated for one year, 1 patient will have a serious bleed (number needed to harm 100) and 5–6 patients will avoid a stroke they would otherwise have suffered (NNT 18–20).

For patients in stable sinus rhythm, the decision regarding anticoagulation becomes more difficult. Reasons include the lower risk of thromboembolism and, more important, the lack of an RCT directly addressing this question (53). A decision to treat such patients therefore depends on observational studies and generalizations from trials for patients with atrial fibrillation. A decision analysis addressing this issue suggested that patients with severe heart failure, for whom taking warfarin is not problematic and whose bleeding risk is low, will benefit from anticoagulation (54). A conservative “do no harm” approach would withhold anticoagulants pending the conduct of an RCT directly addressing this issue.

Non-pharmacologic Therapy

Heart transplant provides a last resort option for some patients with severe heart failure. A randomized trial has shown that a ventricular assist device decreases mortality and improves quality of life over the period of one year, for patients with severe heart failure (55). Differences in survival between groups were no longer significant at 2 years.

The last decade has seen a growing interest in exercise rehabilitation for patients with heart failure. A systematic review of studies of exercise capacity identified 14 parallel group RCTs and 8 randomized cross-over studies. The results suggest short-term improvement in quality of life for heart failure patients participating in exercise programs (56). The participants, however, were not representative of most patients in the community, in that they were younger and had minimal co-morbidity. Much larger trials will be required to determine effects on hospitalizations or mortality.

Organizing care for a patient with severe heart failure is both challenging and crucial. A systematic review of randomized clinical trials of disease management programs for patients with heart failure identified 11 RCTs involving 2,067 patients with heart failure. Overall, the interventions reduced hospitalizations (RR 0.87, 95% CI 0.79–0.96), but not all-cause mortality (RR 0.94, 95% CI 0.75–1.19) (57). The results, however, differed across interventions. Specialized follow-up by a multidisciplinary team led to a substantial reduction in the risk of hospitalization (RR 0.77, 95% CI 0.68–0.86, n=1,366), whereas trials employing telephone contact and improved coordination of primary care services failed to find any benefit (RR 1.15, 95% CI 0.96–1.37, n=646). Disease management programs were cost saving in 7 of the 8 trials that reported cost data. An RCT of a nurse specialist program published subsequent to this systematic review showed consistent results, with a substantial reduction in a combined endpoint of death and hospitalization (hazard ratio 0.61, 95% CI 0.33–0.96) (58).

These results emphasize the importance of compliance-enhancing maneuvers and intensive follow-up for patients with congestive heart failure (CHF). A systematic review of 116 RCTs of compliance-enhancing maneuvers further reinforces the message (59). No single category of intervention was superior, but comprehensive interventions combining education (individual or group; oral, written, or audiovisual presentations), behavioral (packaging, mail or telephone reminders) and affective (home visits and family support) components were more effective than single-focus interventions.

Individualizing the Care of the Heart Failure Patient

In our discussion, we have placed great emphasis on RCTs and meta-analyses of RCTs. Yet, heterogeneity of patient response limits the usefulness of positive RCTs: is our patient a non-responder to an intervention that benefits only some of the target population? For interventions directed at evaluating and preventing distant events such as death or hospitalizations, an entire population must be treated since identifying individual responders and non-responders is never possible. However, when the question concerns symptomatic benefit or possible side effects, individualizing therapy becomes a possibility.

Clinicians traditionally respond to these latter situations with trials that institute, or withhold, therapy. Often, however, bias may intrude in deciding whether there is a causal connection between the intervention and the target outcome. Particularly when symptoms are the issue, natural history, expectations, placebo effects, and the patient's desire to please may all contribute to spurious inferences (60).

A methodology exists for making strong inferences about intervention effects for an individual patient (61). The approach, called "N of 1" RCT, involves pairs of treatment periods in which the patient receives active treatment during one period of each pair, and a matching placebo during the other period (Fig.). The treatment target, most often a symptom or group of symptoms, is monitored quantitatively during each period. Pairs of treatment periods are repeated, until both the patient and clinician become convinced of the treatment's effect or lack of effect. Utilizing the full methodology is challenging, but individual components can be more easily implemented. Repeatedly introducing and withdrawing a treatment, and quantitating patient symptoms, will strengthen inferences about the intervention's impact.

How might such an approach benefit patients with heart failure? Digoxin varies in its impact on symptoms; N of 1 trials can resolve the issue of symptomatic benefit for individual patients. For patients for whom one might hesitate to prescribe beta-blockers because of possible adverse effects on symptoms (such as patients with chronic airflow limitation or relative bradycardia), one can test the impact of the drug in an N of 1 RCT. For patients suffering from concomitant angina despite beta-blockers and nitrates, one can use N of 1 methods to determine the symptomatic impact of adding a calcium-channel blocker, such as amlodopine, without negative cardiac effects in heart failure (62).

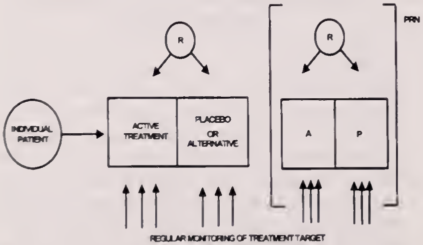

Fig. A schematic representation of an N of 1 randomized trial. The arrows represent measurements of the target outcome, generally patient's symptoms. The "PRN" represents the possibility of repeating the pairs of treatment periods until both patient and physician are satisfied that the patient does, or does not, benefit.

Conclusion

Heart failure patients who place a high value on prolonging life, and who have no contraindications, will wish to take both ACEI and beta-blockers, and may well choose to take spironolactone as well. Digoxin will benefit patients who wish to lower a high risk for hospital readmission. Patients interested in maximizing their quality of life will want to take advantage of exercise programs if they are offered in their community. If possible, a multidisciplinary team should co-ordinate the care of heart failure patients, with likely consequences of reduced hospitalization and reduction in costs.

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Depression in Autopsy-Confirmed Dementia with Lewy Bodies and Alzheimer's Disease

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Abstract

Depression has frequently been cited as a manifestation of dementia with Lewy bodies (DLB). Previous studies have suggested an increase of depression in patients with DLB, compared to those with Alzheimer's disease (AD). The purpose of this study was to examine depressive symptomatology in nursing home residents, from a consecutive series of DLB (n=16) and AD (n=39) autopsy-confirmed cases. Subjects received standard neuropathological analysis and postmortem chart review for clinical assessment of depression. Depressive symptomatology did not differ between the AD and DLB groups, and there was no significant relationship between depression and cortical or subcortical Lewy body (LB) count in the locus ceruleus or substantia nigra. This study suggests that the presence or absence of depression cannot be used to distinguish between AD and DLB. Furthermore, depressive symptomatology in DLB does not appear to be related to severity of cortical or subcortical LB pathology.

Key Words: Dementia, depression, Lewy bodies, Alzheimer's disease, autopsy.

Introduction

DEPRESSION IS RELATIVELY COMMON in dementia, but its prevalence may vary as a function of dementia subtype. In dementia with Lewy bodies (DLB), a disorder characterized by the presence of cortical Lewy bodies, depressive symptoms have been posited to be more characteristic, perhaps distinguishing it from Alzheimer's disease (AD) (1–5). Prevalence estimates of depression associated with DLB have ranged from 20–65% (2–4), compared with 11–35% in AD (2, 3, 6, 7). However, studies that have directly compared depressive symptomatology between AD and DLB have been inconsistent. Some have demonstrated no difference between the two groups (5, 8–12), while others have found that depression is more common in DLB (1–4, 12, 13). As most efforts in characterizing DLB have focused on distinguishing it from AD, an important question is whether depression should be included as a distinguishing feature between the two disorders.

Equivocal findings in the literature may be a result of a number of factors. One recent study noted, for example, that depression may vary with dementia severity (14). The authors examined a large cohort of autopsy-confirmed AD and DLB patients and found that depression was more common in moderately demented DLB patients compared to moderately severe AD patients; no significant differences in depression occurred in the mild and in the severely demented groups. Furthermore, reported depression rates in DLB samples have been relatively consistent across studies, while reported depression rates in

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comparison AD groups have been quite variable, suggesting that results from some studies that have found greater rates of depression in DLB than in AD may be a result of underreporting of depression in AD rather than actual increased depression rates in DLB subjects (2, 3).

Additional factors that may explain discrepancies in findings include variability in demographic features of study subjects (e.g., age at death) and bias in referral source. In one study that found higher rates of anhedonia and anergia in DLB compared to AD, the DLB group was significantly younger than the AD group at the time of initial assessment and autopsy (5). In addition, since referral sources for study cohorts have included hospitals, outpatient clinics, long-term care settings and psychiatric units, patient referral source is a potential bias in studies of DLB. Studies that have relied on the inclusion of patients referred from psychiatric hospitals, for example, may have led to an increased number of reported psychiatric symptoms compared with a more general population of DLB patients (15).

If depressive symptoms are indeed an intrinsic component of DLB, a relationship between the degree of Lewy body pathology and depressive symptoms would be expected. Examination of the relationship between dementia and clinical symptomatology has been a common approach to elucidating the neuropathology underlying clinical presentation. For example, Haroutunian and colleagues (16) used correlational approaches to establish that Lewy body (LB) pathology and plaque pathology independently contribute to cognitive symptom severity in dementia. Studies that have examined depression in DLB have not considered the relationship between depressive symptomatology and LB pathology. Establishing whether there is a specific relationship between the severity of the neuropathology of DLB and the severity of the depressive symptomatology in clinical symptom presentation is important in determining whether depression is intrinsic to DLB. In the examination of the DLB as a cortical dementia, this study considered cortical LB pathology as a pathological correlate of depression. Furthermore, subcortical LB pathology is considered to be in the locus ceruleus and substantia nigra, as these nuclei have been implicated both in the neurobiology of dementia (17–19) and the neuropathology of depression (20).

Studies of clinical correlates with autopsy-confirmed cases typically rely on relatively small sample sizes. Problems associated with the use of small sample sizes are particularly relevant to studies investigating clinical correlates of DLB, since differences between DLB and other dementia subtypes may be quite subtle, requiring a greater amount of statistical power to detect differences. Small sample sizes, therefore, run the risk of inflating type II errors. There has been a recent emphasis on calculating effect sizes in studies that examine brain and behavior relationships, in addition to the statistical tests traditionally reported in hypothesis-driven research (21). In our review of the literature, however, we did not identify a single study comparing AD and DLB patients on depression that reported effect sizes. Thus, it is unclear if negative findings in the literature have been due to insufficient power to detect real differences.

The aim of the current work was to compare incidence of depression in aged nursing home residents with pathologically confirmed AD and DLB. The design of the study allowed for both the comparison of severity of depressive symptomatology and for the comparison of proportion of subjects who met diagnostic criteria for either major or minor depression. A secondary goal of the study was to examine whether severity of depressive symptoms is related to severity of cortical Lewy bodies pathology, in order to further establish whether depression is an intrinsic feature of DLB.

Methods

Neuropathological Assessment

Brain specimens were obtained from a series of 273 consecutive autopsy cases. Subjects had been residents at the Jewish Home and Hospital (JHH) in the Bronx and Manhattan, New York, a standard nursing home care facility which houses elderly individuals with and without dementia. Brain donations were sought by JHH clinical staff and made by next-of-kin consent. Standardized neuropathological studies were conducted on the right hemisphere, after division of the brain specimens at the midsagittal level, as previously described by our group (16, 22). Briefly, hematoxylin-eosin, modified Bielschowsky, modified thioflavin S, anti-J amyloid, anti-tau, and anti-ubiquitin (Dako

Corp, Carpinteria, CA) were used to stain sections from paraffin-embedded blocks; the immunohistochemical method used was an avidin-biotin staining procedure with diamnobenzidine detection. Neuropathological assessment of severity of LB pathology was conducted in two ways. The first was with the Consortium to Establish a Registry for AD (CERAD) neuropathological battery (23), which included assessment of LBs in multiple high-power fields. Pathology ratings were made on a four-point scale (0=absent, 1=sparse, 2=moderate, and 3=severe) in midfrontal cortex, superior midtemporal gyrus, inferior parietal lobule, occipital visual cortex, substantia nigra, nucleus basalis of Meynert, locus ceruleus, and dorsal ventral nucleus of thalamus. For the purposes of this study, only ratings for the locus ceruleus and substantia nigra were included. In a subset of cases, a more quantitative estimate of cortical LB pathology was made by taking the sum of the direct LB count in three neocortical regions (i.e., superior/midfrontal gyrus, orbital frontal cortex and superior temporal gyrus), and in the anterior cingulate gyrus. The pathologist was blind to the clinical ratings of depression and the demographic characteristics of the subject, except for age.

Clinical Assessment

As part of a formal postmortem chart review (PMCR), depressive symptomatology was assessed using a 16-item checklist based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (24) criteria for major depression. Specifically, a clinically trained rater carefully reviewed available data from JHH clinical records, which included admitting diagnoses, neurological and psychiatric consultation reports, nurses' notes, social work records, medication records, mental status testing, and all other medical records and laboratory studies, as reported in previous studies by our group (16, 22). For depressive symptoms, a score of present or absent for each criterion was assigned. The rater was blind to the neuropathological diagnoses. The results of this review were independently confirmed by a psychologist. Symptoms were endorsed as positive if they were present in the medical record. The item was excluded if insufficient information was available to make the rating. Items from the PMCR checklist were then grouped by DSM-IV category (e.g., "significant weight change") and converted to a 9-point DSM-IV depression scale (see Table 1). Each patient's score was determined to be the sum of those items exhibited by the patient. Furthermore, subjects were divided into 3 groups based on their depression checklist score: major depression, minor depression, and no depression. "Major depression" was defined

TABLE 1

Conversion of PMCR Depression Checklist to DSM-IV Depression Checklist

PMCR Depression Checklist	DSM-IV Depression Checklist
1. Depressed mood, dysphoria	1. Depressed mood
2. Decreased interest or pleasure in activities, anhedonia	2. Anhedonia
3. Weight loss without dieting	3. Weight change
4. Decreased appetite	
5. Weight gain or increased appetite	
6. Early insomnia	4. Insomnia or hypersomnia
7. Middle insomnia	
8. Late insomnia, early morning awakening	
9. Hypersomnia	
10. Psychomotor agitation	5. Psychomotor agitation or retardation
11. Psychomotor retardation	
12. Fatigue or loss of energy	6. Fatigue or loss of energy
13. Worthlessness, sinfulness, guilt	7. Feelings of worthlessness or excessive or inappropriate guilt
14. Delusional worthlessness, sin, guilt	
15. Ruminations, inability to concentrate, indecisiveness	8. Diminished ability to think or concentrate
16. Recurrent thought of death or suicide	9. Recurrent thoughts of death or suicidal ideation

PMCR = postmortem chart review; DSM-IV = Diagnostic and Statistical Manual-IV as 5 or more items, of which at least one was depressed mood or anhedonia. "Minor depression" was defined either as 3 or 4 items, of which one was depressed mood or anhedonia. Minor depression was included because of the association with functional disability, increased resource utilization and mortality (25–28). A subject was placed in the category of "no depression" when the number of items ranged from 0–2.

Validity of Postmortem Depression Assessment

An independent sample (n=23) of JHH residents received postmortem assessment of depression symptomatology using the Hamilton Depression Scale (29). The assessment was made by a comprehensive interview with an informant who knew the patient well. Hamilton Depression Scale (HAM-D) items were converted to DSM-IV Depression Checklist scores. An independent postmortem assessment of depression, as described above, was also conducted. To measure validity, the relationship between the sum of the DSM-IV Depression Checklist, derived from HAM-D scores, and the sum of the PMCR checklist scores were examined with Pearson's product moment correlations. As the relationship between the two depression checklist scores was expected to be positive, a one-tailed test was conducted. The significant correlation (r=0.345, p=0.05) indicated adequate validity of the PMCR depression assessment.

In addition to the determination of the depression severity, several other variables were examined. These included gender, age at death, age at placement into JHH, and duration of stay in JHH. Clinical Dementia Rating (CDR) scores were determined for the six months prior to death, as previously described (22).

Subject Selection

Only subjects with a CDR score of 0.5 (questionable dementia) or greater were considered for analysis. Furthermore, subjects were excluded if quantitative assessment of cortical LBs and depression data were not available. The remaining subjects (n=55) represented the final sample and were subsequently divided into two groups based on neuropathological assessment. The AD group (n=39) met CERAD neuropathological criteria for definite AD and did not have any cortical Lewy body pathology. The DLB group (n=16) was defined as those cases in which cortical LB counts were greater than or equal to 1. This group contained both subjects with significant AD pathology (n=10) and subjects without significant AD pathology (n=6). The cohort in this study was part of a larger, ongoing clinical study of normal aging and early dementia.

Results

The AD and DLB groups did not differ in dementia severity, gender, age at admission to nursing home, or age at death (Table 2).

TABLE 2

Demographic Comparison Between AD and DLB Subjects

	AD n=39	DLB n=16	p
Age at admission (years)	83.74 ± 7.49	81.96 ± 5.96	0.40
Percent women	77	69	0.53
Dementia severity (median CDR)	3	4	0.34

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; CDR = Clinical Dementia Rating

Independent samples t-tests were conducted to compare the depression scale scores between the AD (mean score ± SD = 2.08 ± 1.95) and DLB (mean score ± SD = 2.69 ± 1.96) groups. The two groups did not significantly differ: t(53) = –1.05, p=0.297. Effect size for this analysis, using Cohen's *d* (30), was 0.313. According to Zakzanis's (21) interpretation of Cohen's (30) idealized population distribution, an effect size of 0.313 would indicate no effect, with approximately 78.7% overlap of depression scores between the two groups. The distribution of depressive symptomatology was compared between the two groups using Pearson's chi-square analysis for each item of the depression checklist. There were no statistically significant differences for any item; Table 3 displays the distribution of depressive symptoms. When percentages of subjects who met criteria for minor depression, major depression, or no depression were

TABLE 3
Depressive Symptom Distribution for AD and DLB Patients

Symptom	AD (n=39) n (%) meeting criterion	DLB (n=16) n (%) meeting criterion	p
Depressed mood	17 (44%)	8 (50%)	0.67
Anhedonia	9 (23%)	5 (31%)	0.53
Weight change	17 (44%)	11 (69%)	0.09
Insomnia or hypersomnia	5 (13%)	3 (19%)	0.57
Psychomotor agitation or retardation	21 (54%)	11 (69%)	0.31
Fatigue or loss of energy	4 (10%)	2 (13%)	0.81
Feelings of worthlessness or excessive or inappropriate guilt	3 (18%)	1 (6%)	0.85
Diminished ability to think or concentrate	13 (33%)	7 (44%)	0.47
Recurrent thoughts of death or suicidal ideation	1 (3%)	0 (0%)	0.52

AD = Alzheimer's disease; DLB = dementia with Lewy bodies

compared, there were no significant differences between the groups (chi-square=1.662, p=0.436). Sixty-one percent of AD patients were not depressed, 18% met criteria for minor depression, and 21% met criteria for major depression; 44% of the DLB subjects were not depressed, 31% met criteria for minor depression, and 25% met criteria for major depression. Minor and major depression were then considered together (i.e., "depressed") and percentages of subjects who met this criterion for depression were compared. The difference between AD subjects and DLB subjects did not reach statistical significance (chi-square=1.46, p=0.227), with an extremely small effect (Cohen's *d*) of 0.054.

Within the DLB group the relationship between cortical and anterior cingulate LB pathology (i.e., sum count) and depressive symptomatology was examined with Pearson's Product Moment correlation. Cortical LB count and the depression checklist score did not significantly correlate (r=0.162, p=0.237). Similarly, the relationship between CERAD LB severity ratings in locus ceruleus and substantia nigra, and depression checklist scores was examined using Spearman's rank order correlation. The relationship between severity ratings and depression checklist scores did not reach statistical significance for any of these regions (r=0.012, p=0.963 and r = –0.006, p=0.982, respectively).

Discussion

This study examined whether depressive symptoms distinguished between very old, autopsy-confirmed AD and DLB nursing home residents. Depressive symptoms did not significantly differ between these two groups, either by item, or when expressed in symptom clusters defined as major or minor depression. Additionally, in DLB patients, there was no significant relationship between depressive symptoms and distribution of Lewy body pathology or between depression and number of cortical Lewy bodies.

Depressive symptoms are common in DLB and AD, with the literature reporting prevalence rates from 11–35% in AD and 20–65% in DLB. Our results of 21% prevalence of major depression in AD and 25% in DLB are consistent with these findings. When the threshold for depressive symptoms was reduced to include "minor" depression, the prevalence rates of any depression (i.e., minor or major) in our sample was 39% in AD and 55% in DLB. The absolute percentages were higher in the DLB group but did not differ significantly from the AD group, raising the possibility of insufficient power to detect real differences. Our method of characterizing depression in AD and DLB patients yielded similar depression rates, as reported in the literature (2–4). This finding supports the validity of the depression rating method used in this study.

The findings in this relatively older cohort (mean age of over 80 years) of demented nursing home patients may be more generalizable to the overall population of dementia subjects than studies with younger or less severely demented patients. The sample was very well characterized neuropathologically, with accepted criteria for the neuropathological diagnoses of AD and DLB (1). Our clinical measures of depression were retrospective, based on postmortem chart review by trained clinicians. The limitation of retrospective chart review has been present in all of the clinical neuropathological studies comparing rates of depression in AD and DLB patients. A prospective study would have the advantage of more precise clinical characterization and examination of whether the time course in the development of depressive symptoms is different between these two dementia subtypes. Our patients were not new to the nursing home when they died (time spent in nursing home was 3.27 ± 3.16 years), so the stresses of adjustment to the new environment would not be expected to be a major contributor to the development of depressive symptoms in either of the dementia groups.

The patients in our cohort were similar in dementia severity, a quality not shared by all other clinical-neuropathological studies in this area. Differences in dementia severity between groups may have confounded results in other studies. For example, the more severely demented patients may have increased psychosocial stressors, more severe neuropathological changes and increased degrees of medical comorbidity. These factors may influence the presentation of depressive symptoms, independent of dementia subtype.

This study relied on chart review and, indirectly, the documentation practices of the nursing home staff. The depression rates are in the expected range that has been reported in the nursing home setting. Depression rates in the nursing home have historically been underrecognized (31, 32). We would not expect there to be a selective underreporting of depression in the DLB patients that would explain our differences from those studies that reported higher rates of depression in the DLB cases. In fact, if DLB patients have a higher prevalence of behavioral manifestations, some of the disturbances may erroneously be diagnosed as depression. This hypothesis of an overreporting of depressive symptoms in the DLB patients may be one explanation for the studies that did find an increase in depressive symptoms in DLB compared to AD groups.

Differences between our findings compared with those that found higher rates of depression in the DLB patients might also be attributed to differences in referral source. For example, some studies recruited patients from inpatient geriatric psychiatric units, which may have relatively high rates of depression compared to other referral sources. Our subjects were referred from the nursing home facility.

Depression in the elderly may have an atypical presentation (e.g., more anxiety and somatic complaints and less depressed mood), which results in failure to meet DSM-IV criteria for a diagnosis. Thus, if the number of reported depressive symptoms is decreased, then minor depressive symptoms may actually reflect a major depression because of the threshold effects for number of symptoms required. In this study, minor depression was found in 31% of the DLB group compared to 18% of the AD group. The difference was not statistically significant. If this difference is a false negative due to inadequate sample size, then future studies with greater power will be required to bear this out.

Our study included patients with average dementia levels in the moderate-to-severe range and does not answer the question of whether the rates of presenting depressive symptoms differ between AD and DLB groups. There is evidence that first onset depression in later life may be a harbinger for dementia (33), but this has not been prospectively examined for patients who eventually reach autopsy and have confirmed DLB.

Depression may be an epiphenomenon of dementia in general, not specific to dementia subtype (DLB or AD). Depressive symptoms, relatively common in both dementia subtypes, may be a reaction to having a dementia and the attendant psychosocial stressors and functional deficits. This hypothesis is in opposition to the view that depression is a direct manifestation of the pathology underlying the specific dementia subtype. Alternatively, the neuropathology underlying dementia may be distinct from the neuropathology underlying depression in dementia. For example, in AD patients as compared to normal controls, there is an increased degeneration of pigmented brainstem nuclei, decreased levels of cortical norepinephrine and decreased amounts of serotonin metabolites in cortical and subcortical brain regions. These changes have been shown to correlate with depressive symptoms in patients with dementia (34, 35). The neuropathological correlates of depression in DLB are not as well described, but the presence of Lewy bodies in the cortex and brainstem nuclei are postulated to alter affective functioning (18). Furthermore, the neurochemical substrates in depression appear to differ from the neurochemical changes in dementia (36).

The neuropathological changes in both AD and DLB may disrupt the functional circuitry involved in mood regulation, explaining the relatively common occurrence of depression in both conditions. Although there was no observed relationship between LB location or severity and depressive symptoms, the presence of LB pathology may increase the risk of developing depressive symptoms, which would explain the common occurrence of depression in DLB and AD (14). Depressive symptoms may also increase the risk of institutionalization of DLB patients as compared with AD patients (37), possibly explaining a selection bias that results from using pathologically confirmed cases from the nursing home setting. That is, perhaps DLB patients are overrepresented in the nursing home and thus overrepresented in the samples that come to autopsy.

Cholinergic deficits are present in both AD and DLB, with some evidence that the cholinergic deficits in DLB are more pronounced (14, 18, 32, 38). Cholinergic overactivity may contribute to the presentation of depression (39) and perhaps the depressive symptoms in DLB are less pronounced than they would otherwise appear if cholinergic tone were preserved. This hypothesis could be tested when larger numbers of both AD and DLB patients are treated with cholinesterase inhibitors, effectively raising the cholinergic tone. In addition to changes in cholinergic function, deficits in noradrenergic, serotoninergic and dopaminergic tone have been reported in depression associated with dementia. The present study was not designed to compare neurochemical differences between dementia subtypes. Further prospective work may attempt to correlate neurochemical changes with depressive symptoms in the various dementia subtypes.

This study found no significant relationship between distribution of LB pathology and depressive symptomatology in DLB patients. This suggests that depression may not be intrinsic to DLB.

The study's limitations include the dementia severity of the residents, the use of a retrospective chart review and relatively small sample sizes. The strengths of the study include the use of effect size analyses to reduce the probability of a type II error. Nursing home subjects with dementia may have improved generalizability compared to referral sources in other studies. Finally, the DLB and AD subjects did not significantly differ in demographic features and were neuropathologically well characterized.

Summary

Depressive symptoms do not distinguish between older moderately-to-severely demented AD and DLB nursing home residents, and depressive symptoms do not appear to be intrinsic to DLB. However, the relatively high rates of depression in both dementia subtypes should prompt clinicians and caregivers to recognize and address this important contributor to excess disability.

Acknowledgments

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The Surgical Management of Severe Obesity

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Abstract

The prevalence of obesity in the United States is increasing to epidemic proportions. At present, more than 60% of Americans are overweight. While a variety of medications are available for the treatment of obesity, none results in the long-term loss of more than 10% of body weight. The current standard for the treatment of severe obesity, defined as a body mass index of greater than 35–40 kg/m^2, is surgical. Several surgical procedures are currently available, including gastric bypass, biliopancreatic diversion with duodenal switch, and the adjustable gastric band. These operations may be performed using laparoscopic surgical techniques to minimize perioperative morbidity and postoperative recovery time. To optimize the outcome of this type of procedure, bariatric surgery should be performed on carefully selected patients, in centers specially equipped to care for the obese, within a broadly based, multidisciplinary setting providing lifelong postoperative care.

Key Words: Severe obesity, morbid obesity, obesity, bariatric surgery, gastric bypass, biliopancreatic diversion, adjustable gastric band.

Introduction

THE PREVALENCE OF OBESITY in the United States has increased to epidemic proportions over the last decade. Between 1991 and 1998 the percentage of Americans meeting the clinical definition of obesity increased from 12.0% to 17.9% (1). This change has been identified in all 50 states, across all age groups, races, and educational levels. And obesity has been identified as a major risk factor for many diseases, including cardiovascular disease, cancer, and type II diabetes (2). Actuarial data suggest that more than 300,000 deaths per year in the United States may be attributed (to some extent) to obesity (3).

The costs associated with the treatment of obesity are similarly extreme. In the United States, more than $30 billion per year is spent on dietary and behavioral treatments for obesity. A study of Kaiser Permanente patients revealed health care costs to be 44% greater among severely obese patients (4). While the problem of obesity is an international one, the effects are especially acute in the U.S., where the cost of treating obesity and related ailments has been estimated to account for fully 7% of the national health care budget (5).

Unfortunately, the options available for the treatment of this vast public health problem are relatively limited. Dietary and behavioral approaches to obesity have achieved very limited success. While several anti-obesity drugs are available, these rarely result in the loss of more than 10% of total body weight.

At present, the only available therapeutic intervention that provides effective long-term weight loss for the severely obese is bariatric surgery. Recent advances in surgical technique have allowed bariatric procedures to be performed using laparoscopic, minimally invasive techniques, thus reducing hospital stays and minimizing early postoperative morbidity.

Definition of Obesity

The most widely accepted measure of obesity is the body mass index (BMI). This

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number is calculated by dividing a patient's mass in kilograms by the square of his or her height in meters. A normal BMI is considered to range from 18.5 – 24.9 kg/m^2. A BMI between 25.0 and 29.9 is considered overweight. A BMI of 30 or greater is classified as obese; this is further subdivided into Class I, II, or III obesity, as shown in Table 1 (6).

It may be important to consider other factors besides the BMI, such as total muscle mass and waist circumference. An extremely muscular individual may have an elevated BMI without being considered overweight. Waist circumference has been shown to be an excellent indicator of abdominal fat mass (7). A circumference greater than 88 cm (35 in) in women or 102 cm (40 in) in men strongly correlates with an increased risk of obesity-related disease (6).

Prevalence of Obesity and Obesity-Related Morbidity

Obesity, defined as a BMI greater than 30 kg/m^2, has become a worldwide problem. A recent report from the World Health Organization stated that the number of obese adults worldwide had increased to more than 300 million in the year 2000 (8). And the results of the 1999 National Health and Nutrition Examination Survey (NHANES) revealed that 61% of American adults were overweight (BMI $\geq$ 25.0 kg/m^2), and 26% obese (BMI $\geq$ 30.0 kg/m^2) (9). But a 1999 study by the American Cancer Society demonstrated that the relative risk of death for obese men was 2.58 times that of controls (1). Thus, elevated BMI has been identified as an independent predictor of early death.

TABLE 1
Categories of Obesity

	BMI (kg/m^2)	Risk
Underweight	<18.5	Increased
Normal	18.5 – 24.9	Normal
Overweight	25.0 – 29.9	Increased
Obesity Class I	30.0 – 34.9	High
Obesity Class II	35.0 – 39.9	Very high
Obesity Class III	≥40.0	Extremely high

Data taken from National Institutes of Health (NIH); National Heart, Lung and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults — the evidence report. www.nhlbi.hih.gov/guidelines/obesity/ob_gdlns.pdf on p. 16.

Behavioral and Dietary Management

It is widely appreciated that weight loss can be obtained by decreasing caloric intake (dieting) and increasing metabolic activity (exercising). Decreasing caloric intake by 500 – 1000 kcal/day below maintenance level can result in the loss of 0.5 kg of body weight per week (10). However, while 29% of men and 44% of women state that they are trying to lose weight, only 20% of these men and women report that they are actually implementing such behavioral and dietary modifications (11).

Perhaps the explanation for this failure of behavior to follow data lies in the knowledge that weight-reduction programs based on dieting and exercise alone are frequently ineffective. Some 90 – 95% of persons who lose weight go on to regain the weight lost — and gain more (10). Nonetheless, Americans continue to spend $30 billion per year on weight-loss programs and diets (12).

Medical Management

Substantial enthusiasm for the pharmacologic treatment of obesity was generated in 1992, when Weintraub published data on the use of medical therapy used in combination with behavioral management (13). Each medication discussed in that study, fenfluramine and phentermine, serves to reduce appetite. Fenfluramine produced moderate amounts of weight loss on a short-term basis; however, it was removed from the market when evidence emerged that is was associated with valvular heart disease.

Currently, two weight-reduction medications are available for long-term use in the U.S. Sibutramine (Meridia®) (Abbott Laboratories, Abbott Park, IL) is an appetite suppressant that works by inhibiting the reuptake of norepinephrine, serotonin and dopamine. While it appears to be a safe medication, its efficacy is quite limited. One study showed that subjects treated with sibutramine lost only 4 kg more than those treated with placebo (14). In a second study, only 13% of subjects treated with sibutramine lost more than 10% of their body weight, versus 4% of those treated with placebo (15).

The second medication currently available for long-term use is orlistat (Xenical®) (Roche, Nutley, NJ), a synthetic lipase inhibitor. Orlistat binds to lipases in the gut and inhibits the absorption of dietary fat. While it appears to be a fairly safe medication, its efficacy is similarly limited. Only 20–40% of subjects on orlistat lost 10% or more of their initial body weight, versus 10–25% of control patients treated with placebo (16).

Surgical Management

In 1991, the National Institutes of Health (NIH) organized a consensus conference to examine the role of both surgical and nonsurgical interventions in the treatment of severe obesity. The consensus panel ultimately recommended that the most appropriate treatment for a severely obese patient who had failed dieting, exercise, and behavioral management was surgical therapy. The panel recommended (17) that these patients should be "selected carefully after evaluation by a multidisciplinary team with medical, surgical, psychiatric and nutritional expertise" and operated on "by a surgeon substantially experienced with the appropriate procedures and working in a clinical setting with adequate support for all aspects of management and assessment."

Appropriate patient selection was one of the central points contained in the consensus panel's recommendations. Patients with a BMI greater than 40 kg/m^2 were considered to be good candidates for a bariatric procedure because of the substantial negative impact of obesity on their quality of life. Certain patients with BMIs between 35 and 40 were also classified as candidates for surgical therapy if they suffered from one or more comorbidities caused by their obesity, such as sleep apnea, Pickwickian syndrome, or diabetes mellitus.

At the present time, a number of different surgical procedures are available for treatment of the severely obese patient. These procedures generate weight loss from two mechanisms of action: restriction and malabsorption. Because the different operations entail substantially different lifestyle modifications, it is essential that patients are well informed about the specific changes in lifestyle, eating habits, and bowel habits that may accompany the procedure being suggested for them.

Gastric Bypass

The gastric bypass is the most commonly performed weight loss operation in the U.S. and has earned the reputation of being the "gold standard" against which other procedures are compared. First reported in 1967 by Mason, the gastric bypass has undergone numerous modifications (18). Most current techniques involve the use of a surgical stapler to create a small, vertically oriented stomach pouch based on the lesser curvature. The pouch, typically 15–30 cc in capacity, is anastomosed to a segment of small intestine in a Roux-en-Y fashion (Fig. 1). Ingested food passes from the stomach pouch through the gastrojejunostomy into the alimentary limb, typically between 50 and 150 cm long.

The gastric bypass provides a substantial amount of dietary restriction. The restriction is created by the small stomach pouch, which gives the patient a feeling of satiety after eating a small meal. In addition, the gastric bypass provides a small-to-moderate degree of intentional malabsorption due to the separation of food, which passes through the alimentary limb of the Y, from the biliopancreatic secretions, which pass through the biliopancreatic limb of the Y. The degree of malabsorption can be adjusted by modifying the length of the alimentary and biliopancreatic limbs (19).

Some patients may experience the "dumping syndrome" upon ingestion of sweets, after gastric bypass surgery. This is caused by the rapid passage of gastric pouch contents directly into the small bowel, unimpeded by a pyloric valve. The presence of concentrated simple sugars in the Roux limb presents a substantial osmotic load that may result in cramping and abdominal discomfort; additionally, the ensuing rapid release of insulin by the pancreas may cause symptomatic

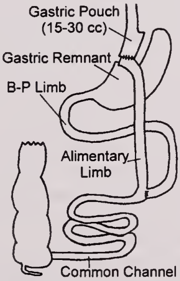

Fig. 1. The Roux-en-Y gastric bypass procedure. B-P limb is biliopancreatic limb. Illustration ©2002 Daniel M. Herron, http://www.surgicallyslim.com/gastric_bypass.htm. Accessed 4/14/03.

hypoglycemia. This unpleasant reaction to sugars is considered to be a desired aftereffect of gastric bypass surgery, and has been referred to by patients as the "postoperative police officer."

Weight loss after gastric bypass has been shown to be greater than that obtained by dietary, medical, behavioral, or combined approaches to weight loss. A recent long-term follow-up study performed by MacLean et al. defined postoperative success as a reduction in weight to a BMI of less than 35 kg/m^2. By this criterion, a successful outcome was achieved in 93% of patients whose initial BMI was less than 50 kg/m^2, and in 57% of those with an initial BMI greater than 50 kg/m^2 (20).

In 1996 a gastric bypass procedure using laparoscopic techniques was first reported (21). In a number of studies since that time, the laparoscopic approach has been shown to combine the efficacy of the open approach with the decreased pain, lower wound morbidity, and shorter convalescence of a minimally invasive procedure (22, 23).

Results of several laparoscopic gastric bypass series have paralleled or improved upon those of open surgery. In Higa's series of 400 laparoscopic procedures, patients lost an average of 69% of their initial excess weight by 12 months after their operations (22). Schauer's group reported even better weight loss; in a group of 275 patients undergoing laparoscopic gastric bypass, there was an average loss of excess weight of 83% at 24 months after surgery (23). In experienced hands, the laparoscopic gastric bypass can routinely be performed in less than 1.5 hours (22). Average hospital stay was quite short in both series: 1.6 days in the former and 3.6 days (median 2) in the latter.

A prospective, randomized trial comparing the results of laparoscopic and open gastric bypass was recently completed (24). Laparoscopic patients were found to have substantially less impairment of pulmonary function after surgery and decreased postoperative pain. In our experience, the convalescence after laparoscopic gastric bypass is substantially reduced relative to open procedures, with some patients returning to work in 2 weeks or less.

The most commonly reported complication of laparoscopic gastric bypass surgery is stenosis of the gastrojejunal anastomosis. This occurs in 5 – 10% or more of patients and is treated by outpatient endoscopic balloon dilatation. Marginal ulcers may occur in approximately 1% of patients due to exposure of the proximal jejunum to hydrochloric acid from the gastric pouch. This is typically managed pharmacologically using proton pump inhibitors. Despite the substantial cardiac, pulmonary and endocrine comorbidities of the typical bariatric patient, perioperative mortality ranged from 0.0 –0.4% (22, 23).

After surgery, patients must remain on a high-protein, low-fat diet, and supplement their diet with multivitamins, iron, and calcium, usually on a twice-a-day basis. Ursodiol (Actigall) may be given to minimize the risk of developing gallstones during the period of acute weight loss (25). Patients must also modify their eating habits by avoiding chewy meats and other foods that may inhibit normal emptying of their stomach pouch. Nutritional and metabolic bloodwork needs to be performed on a frequent basis; in our practice this is performed 3 months, 6 months, and 12 months after surgery, and annually thereafter.

Biliopancreatic Diversion with Duodenal Switch

The first weight loss procedure performed in the U.S. was the jejunoileal bypass (26). This procedure functionally "short-circuited" the small bowel by removing a major portion of small intestine from the alimentary path. The operation allowed the patient to eat normal-sized meals and resulted in excellent weight loss. However, the operation was ultimately abandoned due to excessive long-term nutritional complications, including protein and calorie malnutrition, electrolyte imbalances, renal stone formation and hepatic failure (27).

The desire to create an operation that combined the safety of the gastric bypass with the potentially better lifestyle and weight loss of a malabsorptive operation led Scopinaro to create the biliopancreatic diversion (28). In this procedure an antrectomy is performed, reducing the volume of the stomach to 200 – 500 mL. The remaining stomach is anastomosed to the distal 250 cm of small intestine. The excluded small intestine, containing the bile and pancreatic secretions, is connected to the alimentary channel 50 cm proximal to the terminal ileum.

This procedure was modified by Marceau and Hess to include a "sleeve gastrectomy," in which the greater curvature of the stomach is resected, but the lesser curvature of the stomach and the pylorus remain intact (29, 30). The first portion of the duodenum is divided and connected to the distal 250 cm of the small bowel. The biliopancreatic limb, containing all the bile and pancreatic secretions, is anastomosed 100 cm from the terminal ileum, providing a longer "common channel" and thus more protein and fat absorption than the Scopinaro version of the procedure (Fig. 2). This procedure has been named the "biliopancreatic diversion with duodenal switch" (BPD-DS).

The BPD-DS offers several theoretical benefits over the gastric bypass. Because the volume of the stomach after sleeve gastrectomy is substantially larger than the gastric pouch of the gastric bypass, patients may eat larger portions. Additionally, the dumping syndrome is avoided, since the pylorus remains intact. Almost 60% of patients report that they can "eat whatever they want" after BPD-DS, with 90% "almost never" vomiting (29). However, because of the substantial fat malabsorption obtained with BPD-DS, these patients must consume additional supplements of the fat-soluble vitamins (A, D, E, K) in addition to the supplementation used by the gastric bypass patients.

As with the gastric bypass, laparoscopic techniques have been applied to the BPD-DS. The laparoscopic approach was first utilized in 1999 (31). Early results in this series appeared to be similar to those of open series.

Weight loss after the BPD-DS is excellent. In Marceau's series of 457 patients, patients lost an average of 73% of their initial excess weight. As might be expected, however, patients suffer from substantial side effects of fat and protein malabsorption. Most patients have from 3–4 soft bowel movements per day, and notice a substantial increase in the amount of flatus passed, as well as the strength of its odor. This is reported to be a "major problem" by 30–40% of patients. Abdominal cramping and bloating is also common, reported to occur more than once a week in approximately one-third of patients (29).

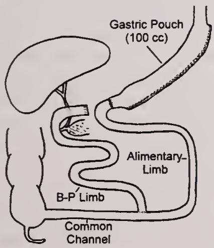

Fig. 2. The biliopancreatic diversion with duodenal switch (BPD-DS). B-P limb is biliopancreatic limb. Illustration ©2002 Daniel M. Herron, http://www.surgicallyslim.com/bpt.ds.htm. Accessed 4/14/03.

Additionally, long-term protein malnutrition occasionally requires readmission to the hospital for supplemental parenteral nutrition or surgical revision. The most commonly performed revision involves lengthening of the "common channel" where the alimentary limb ultimately joins the biliopancreatic limb. The risk of re-hospitalization in Marceau's series was approximately 1% per patient per year (29).

Because the BPD-DS involves a partial gastrectomy and a complicated duodenal dissection, it is considered to be a substantially more complex operation than the gastric bypass. This is reflected in its higher mortality rate, from 0.5–2.5%, and an incidence of major morbidity of over 15% (30, 31). Nonetheless, public interest in the procedure continues to rise, based on the perception of a superior quality of life postoperatively.

Restrictive Procedures

Vertical Banded Gastroplasty

Purely restrictive bariatric procedures function solely by reducing the functional capacity of the stomach. The vertical banded gastroplasty (VBG), commonly referred to as a "stomach stapling," is an example of this type of procedure. In the VBG, a surgical stapler is used to create a vertically oriented pouch based on the lesser curvature of the stomach. The outlet of this pouch is restricted by a prosthetic band. Unlike the gastric bypass, the VBG pouch empties into the stomach, and no rerouting of the alimentary path occurs.

The VBG offers several apparent advantages. It is a technically straightforward procedure, whether performed using open or laparoscopic surgical techniques. It leaves the alimentary tract continuous, thus reducing or avoiding the potential malnutrition issues that may accompany malabsorptive operations such as the gastric bypass or the BPD-DS. Because there are no surgical anastomoses, there is no risk of anastomotic leakage.

Unfortunately, these theoretical advantages have not been supported by the available clinical data. Balsiger recently reviewed the long-term outcome of VBG. Of 70 patients who underwent VBG between 1985 and 1989, only 14 (20%) had experienced a durable loss of more than 50% of their excess weight (32). MacLean performed a prospective randomized trial comparing VBG to gastric bypass, with success defined as a postoperative BMI of less than 35 kg/m^2. Gastric bypass (with a completely separated gastric pouch) was successful in 83% of patients, while VBG provided a successful outcome in only 39% (33).

Laparoscopic Adjustable Gastric Band

Recently, interest in purely restrictive procedures has resurfaced, due to the approval by the Food and Drug Administration (FDA) in June 2001 of a laparoscopically placed adjustable gastric band (Fig. 3). The device (Lap Band, Bioenterics Corp., Carpenteria, CA) consists of a hollow silicone rubber band that can easily be wrapped around the superior portion of the stomach, just distal to the gastroesophageal junction. The amount of restriction may be adjusted by injecting or withdrawing saline solution from the hollow core of the band which can be accessed via a subcutaneous port similar to that used for long-term venous access in chemotherapy patients. In theory, this mechanism allows the amount of restriction to be fine-tuned until an appropriate balance of restriction and lifestyle is achieved.

Results of the adjustable gastric band are quite mixed. Excellent results have been reported from Europe and Australia. A recent French study of 400 patients demonstrated a loss of 50% of initial excess body weight at 2 years follow-up (34). Fielding has reported the results of 355 patients undergoing laparoscopic adjustable gastric banding in Australia. Complication rates were low, and the 58 patients who were followed for 18 months postoperatively lost an average of 62% of their excess weight (35). Confusingly, these data are in marked conflict with American results. DeMaria reported on 37 patients from one of the 8 American centers evaluating the band for FDA approval. These patients lost only 18% of their initial excess weight at 3 – 18 months after surgery. More than 40% of the patients in that series had their band removed, most commonly because of inadequate weight loss (36).

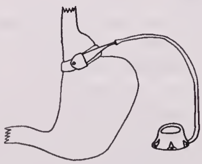

Fig. 3. The laparoscopic adjustable gastric band. Illustration ©2002 Daniel M. Herron.

It is not clear whether the poor results of the laparoscopic adjustable gastric band in the United States are due to differences in the diet, lifestyle and/or compliance of American patients, or if they are statistical anomalies caused by inadequate sample size. While the adjustable band may hold promise, its use in American patients must be considered with caution.

Surgical Weight Loss: Long-Term Health Benefits

There is little debate that surgery can provide greater and longer-lasting weight loss than dietary, behavioral or medical therapy. However, the risks of surgery, while low, are not negligible (Table 2). Thus, when considering a surgical procedure for an individual patient, it is necessary to consider the long-term benefits of substantial weight loss.

Type II diabetes, also referred to as non-insulin-dependent diabetes mellitus (NIDDM), affects approximately 13 million Americans (37). Of severely obese patients, roughly one-third suffer from type II diabetes, and another third have impaired glucose tolerance (38). In a landmark study, Dr. Pories followed the outcome of 608 severely obese patients who underwent gastric bypass, with higher than 97% follow-up. Of the 146 patients with type II diabetes in his study, 82.9% ultimately became euglycemic. The results were even more impressive for patients with impaired glucose tolerance; of the 152 patients in this category, 98.7% became euglycemic after surgery (37).

In a second study, the same research group compared patients undergoing gastric bypass surgery with a control group that did not undergo surgery, due to insurance denial or personal considerations. Mean follow-up ranged from 6 – 9 years. In the group

TABLE 2
A Comparison of Weight Loss Operations

	Gastric Bypass	Biliopancreatic Diversion with Duodenal Switch	Gastric Band
Duration of procedure	1–4 hours	2–5 hours	0.5–2 hours
Length of stay	2–3 days	2–4 days	1–2 days
Postoperative supplements	MVI, iron, calcium	MVI, iron, calcium, ADEK	MVI, calcium
Estimated weight loss	50–75% EBW	60–80% EBW	40–60% EBW
Side effects	dumping syndrome	diarrhea, excessive flatus, body odor changes	vomiting
Short-term complications	DVT/PE, anastomotic leakage, pouch leakage, gastrointestinal bleeding	DVT/PE, anastomotic leakage, pouch leakage, gastrointestinal bleeding	DVT/PE, port-site infection, esophageal perforation
Long-term complications	gastrojejunostomy stenosis, iron deficiency anemia, calcium deficiency, B12 deficiency, marginal ulcer, internal hernia	iron deficiency, calcium deficiency, protein malnutrition, need for common channel revision, internal hernia	band slippage, device leakage, erosion into stomach/esophagus, pouch enlargement, device infection
Mortality rate	0–1%	0.5–2.5%	0–1%

EBW=Excess body weight; MVI=multivitamin; ADEK=Fat-soluble vitamin supplement; DVT/PE=Deep vein thrombosis, pulmonary embolism.

undergoing surgery, the percentage of patients requiring insulin or oral hypoglycemic medication dropped from 31.8% preoperatively to 8.6% postoperatively. In contrast, patients who did not undergo surgery saw their need for hypoglycemic therapy increase from 56.4% at initial contact to 87.5% by the end of the follow-up period (39).

Dyslipidemia is another comorbidity present in a large subset of the severely obese population. Dr. Marceau of Laval Hospital in Quebec reported on 717 patients who had undergone duodenal switch. Preoperatively, 23% of patients suffered from elevated cholesterol (> 6 mmol/L). Postoperatively, this was reduced to 0.7% (29). Marceau noted a substantial, but less extreme, decrease in the incidence of hypertension requiring medical therapy. Preoperatively, antihypertensive medication was required by 91 patients; only 38 required it after a mean follow-up period of 4.1–8.3 years.

Sleep apnea is another potentially disabling problem with a disturbingly high incidence in the severely obese population. It may be caused by compression of the upper airway by fatty tissue, combined with increased upper-airway collapsibility. Schueller and Weider studied 15 severely obese patients with severe sleep apnea, 8 of whom had already been treated with tracheostomy (40). After they underwent a weight loss procedure, their mean respiratory disturbance index (RDI) decreased from 96.9 events/hr to 11.3 events/hr. Minimum oxygen saturation increased from a mean of 58.7% before surgery to 85.2% after surgery. Of the 8 patients with tracheostomies, all were ultimately able to have their tubes removed.

The Management of Severe Obesity: What Does the Future Hold?

Recent discoveries in human fat metabolism have led to renewed hope that an effective pharmacological treatment for obesity may one day be discovered. The peroxisome proliferator-activated receptor (PPAR)-gamma gene has been identified as the potential master regulator of fat cell formation (41). Thus, pharmacologic manipulation of this gene's expression could theoretically downregulate fat cell formation. Angiogenesis inhibitors such as TNP-470, angiostatin and endostatin have been tested on mice in hopes of slowing or stopping neoplastic tumor growth. An interesting side effect has been that these mice have lost nearly half their body weight. While there have been no human studies using these medications for weight loss purposes, the use of these agents has been patented as a potential cure for obesity (42).

However, despite the promise that this and other research shows, surgical intervention currently remains the only effective treatment for severe obesity. For this reason, gastric bypass has been one of the most rapidly increasing surgical procedures performed in the U.S. (personal communication, Sheila Salter, USSC Corp., Norwalk, CT). In hopes of optimizing the conditions under which bariatric surgery is performed, the American College of Surgeons recently released a series (43) of formal "Recommendations for Facilities Performing Bariatric Surgery." Their recommendations include the following points:

- Bariatric surgery should only be performed by a team of experienced surgeons, anesthesiologists, nurses, and nutritionists. Recovery room and nursing staff should be specially trained in the management of the severely obese.
- Operating rooms should be specially designed and equipped to accommodate the unique needs of the severely obese patient.
- Hospital facilities, including intensive care units, radiology departments, and rehabilitation facilities, must be redesigned with the care of these patients in mind.

These requirements for a high-quality bariatric treatment program are demanding. Moreover, patient selection needs to be performed very carefully, and the choice of procedure needs to be tailored to the individual patient's physiologic needs and desires for postoperative lifestyle. Finally, nutritional and metabolic follow-up must continue for the lifetime of the patient. If these requirements are fulfilled, the obese patient undergoing bariatric surgery may look forward to vastly improved health and quality of life.

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In Memoriam

Harriet S. Gilbert, M.D.

The Journal recognizes with deep regret the passing of Associate Editor Harriet S. Gilbert, M.D.

Dr. Gilbert began her distinguished career at Mount Sinai as an intern, and became a hematologist and renowned expert in myeloproliferative diseases. In her many years as an associate editor of *The Journal*, she provided valued expertise, warmth and friendship.

In gratitude and in sadness, *The Journal* extends its sincere condolences to her family.

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VOLUME 71 NUMBER 2 MARCH 2004

CONTENTS

GRAND ROUNDS

Renal Artery Disease: Diagnosis and Management *Jeffrey W. Olin* 73

Induction of Immunity against Human Cytomegalovirus *Thomas Bennekov, David Spector, and Erik Langhoff* 86

The Multidisciplinary Approach to Hemodialysis Vascular Access at The Mount Sinai Hospital *Joseph A. Vassalotti, Abigail Falk, Victoria Teodorescu, and Jaime Uribarri* 94

Current Medical Treatment of Pulmonary Arterial Hypertension *Roxana Sulica and Michael Poon* 103

Neurohormonal Antagonism in Heart Failure: What Is the Optimal Strategy? *Jonathan D. Sackner-Bernstein and David Hart* 115

GENERAL ARTICLES

Intestinal Metastases from Renal Cell Carcinoma: A Rare Cause of Intestinal Obstruction and Bleeding *George M. Pavlakis, George H. Sakorafas, and George K. Anagnostopoulos* 127

Ectopic Intrathoracic Thyroid: Case Report *George H. Sakorafas, Athanasios Vlachos, George Tolumis, George A. Kassaras, George K. Anagnostopoulos, and Dimitrios Gorgogiannis* 131

If I Were Dean: A Challenge to New Medical Students *Jeremy Hugh Baron* 134

Recombinant Interferon Gamma-Ib and Low-Dose Steroid in Two Pediatric Cases of Nonspecific Interstitial Pneumonia *Donato Rigante, Angelica Bibiana Delogu, Gilda Federico, Gabriella De Rosa, and Achille Stabile* 139

Information for Authors i

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Grand Rounds

Renal Artery Disease:

Diagnosis and Management

JEFFREY W. OLIN, D.O.

Abstract

Renal artery stenosis (RAS) is most commonly due to either fibromuscular dysplasia or atherosclerosis. The former predominates in young women while atherosclerosis is usually encountered in individuals over the age of 55. The most common clinical manifestation of fibromuscular dysplasia is hypertension, which can frequently be cured or significantly improved with percutaneous balloon dilation. Atherosclerotic RAS may present with hypertension, renal failure (ischemic nephropathy), recurrent episodes of congestive heart failure and flash pulmonary edema or may be discovered incidentally during an imaging procedure for some other reason.

Screening tests for RAS have improved considerably over the last decade. While captopril renography was utilized almost exclusively in the past, duplex ultrasound of the renal arteries or magnetic resonance angiography has replaced other modalities as the screening test of choice in many centers. Rarely does an arteriogram have to be performed for diagnostic purposes only.

Management of RAS consists of three possible strategies: medical management, surgical management or percutaneous therapy with balloon angioplasty and stent implantation. The treatment of choice to control hypertension in patients with fibromuscular disease is percutaneous angioplasty. Renal artery stenting has replaced surgical revascularization for most patients with atherosclerotic disease who meet the criteria for intervention.

Key Words: Renal artery disease, diagnosis, treatment.

OVER THE LAST DECADE, there has been increased awareness of renovascular disease as a potentially correctable cause of hypertension and renal insufficiency. The association between renal artery stenosis (RAS), coronary artery disease and congestive heart failure (CHF) has been well studied. It is known that there is a markedly decreased survival rate (due to myocardial infarction and stroke) in patients with RAS. Nephrologists have long recognized that RAS may present with acute or chronic renal failure (ischemic nephropathy), at times leading to end-stage renal disease. Because RAS may present with many different clinical manifestations, primary care physicians, cardiovascular specialists, vascular surgeons and nephrologists will encounter RAS with increased frequency.

Incidentally discovered RAS is quite common (1, 2), but renovascular hypertension only occurs in 1–5% of all patients with hypertension. RAS is most commonly due to either fibromuscular dysplasia (FMD) or atherosclerosis. The predominant clinical manifestation of FMD is hypertension that can frequently be cured or significantly improved with percutaneous transluminal angioplasty. FMD predominates in young women, while atherosclerosis is encountered most often in individuals over the age of 55. Approximately 90% of all renovascular lesions are secondary to atherosclerosis (3). Atherosclerotic RAS most often occurs at the ostium or the proximal 2 cm of the renal artery (4). Distal arterial or branch involvement is distinctly uncommon. Atherosclerotic RAS may present with one or more of the following: hypertension, renal failure (ischemic nephropathy), refractory angina, and/or recurrent episodes of CHF and flash pulmonary edema.

Dustan et al. (5) reviewed 149 aortograms and found that approximately half of the patients with greater than 50% RAS did not have hypertension. Moreover, the presence of anatomic RAS does not necessarily establish that the hypertension or renal failure is caused

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by the RAS. Primary (essential) hypertension may exist for years prior to the development of atherosclerotic RAS later in life. Renal revascularization (percutaneous transluminal angioplasty [PTA]/stent, surgery) may result in improvement of blood pressure control in 50–80% of patients but cure is unusual in patients with longstanding hypertension (4, 6–9). Ischemic nephropathy or flash pulmonary edema almost always occurs in the presence of bilateral renal artery disease or disease in a solitary functioning kidney. Percutaneous or surgical revascularization can lead to improvement or stabilization in renal function and improvement in CHF in the carefully selected patient (8–10).

Pathogenesis of Hypertension in Renal Artery Stenosis

A detailed description of the pathophysiological mechanisms of hypertension in RAS is beyond the scope of this article. On a very simplistic level, early in the course of the disease, patients with unilateral renal artery stenosis have a renin-mediated form of hypertension, while patients with bilateral RAS, or stenosis to a solitary functioning kidney, have a volume-mediated form of hypertension (9, 11). In patients who are volume expanded, administration of either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) does not cause a decrease in blood pressure or change in renal blood flow. Functional renal insufficiency may even occur when ACEIs are administered to patients with bilateral RAS or RAS to a solitary kidney, especially in the volume contracted state. However, dietary restriction of sodium or administration of diuretics will return the subject to a renin-mediated form of hypertension, and restore sensitivity to an ACEI or ARB.

Pathophysiology of Ischemic Nephropathy

It is difficult to fully understand the nature of ischemic nephropathy. This is due to several factors: (a) there is no linear relationship between the degree of renal artery stenosis and the degree of renal dysfunction (11); (b) it is not easy to determine with certainty whether stenosis of the main renal artery is causing the renal insufficiency or whether parenchymal disease is the culprit; and (c) some patients undergoing renal revascularization (PTA/stent/surgery) demonstrate worsening renal function after the procedure. This may be due to atheromatous embolization caused by the procedure, or to the natural history of the underlying disease that caused the problem in the first place. It should be emphasized that patients who develop azotemia while receiving angiotensin-converting enzyme inhibitors or ARBs have bilateral RAS, RAS to a solitary kidney, or decompensated CHF in the sodium-depleted state (12–17).

There are two mechanisms by which renal functional impairment may occur with the use of antihypertensive agents. The first mechanism can be caused by any antihypertensive agent, when a critical perfusion pressure is reached below which the kidney no longer receives adequate perfusion. This has been shown by the infusion of sodium nitroprusside in patients with high-grade bilateral RAS (13). When the critical perfusion pressure was reached, the urine output, renal blood flow, and glomerular filtration rate declined and later returned to normal when the blood pressure increased above this critical perfusion pressure. The exact pressure necessary to perfuse a kidney with RAS varies with the degree of stenosis and is different in different patients.

The second mechanism is confined to patients receiving ACEI or ARB agents and may or may not involve significant change in blood pressure (12, 14). Patients with high-grade bilateral RAS or RAS to a solitary kidney may be highly dependent on angiotensin II for glomerular filtration. This is particularly common in patients who receive a combination of ACE inhibitor and diuretic (18), or in patients who are placed on a sodium-restricted diet (19). Under these circumstances, the constrictive effect of angiotensin II on the efferent arteriole allows for the maintenance of normal transglomerular capillary hydraulic pressure, thus allowing glomerular filtration to remain normal in the presence of markedly diminished blood flow. In this instance, glomerular filtration is highly dependent on angiotensin II. When an ACEI is administered, the efferent arteriolar tone is no longer maintained and glomerular filtration is therefore decreased. A similar situation occurs in patients with decompensated CHF who are sodium depleted (16).

Clinical Manifestations of Renal Artery Disease

Prevalence

In a recent population-based study, Hansen and colleagues have reported on the prevalence of renovascular disease in a cohort of 834 elderly patients (20), participants of the Cardiovascular Health Study, who underwent renal duplex ultrasound. Fifty-seven (6.8%) had anatomic renal artery stenosis. There was no difference in the prevalence of RAS in whites (6.9%) compared to African Americans (6.7%).

Several series have looked at the prevalence of renovascular disease in patients who have atherosclerotic disease elsewhere. To determine the prevalence of atherosclerotic RAS, we studied 395 consecutive patients who had undergone arteriography as part of an evaluation for an abdominal aortic aneurysm, aortoiliac occlusive disease, and peripheral arterial disease (Table 1) (1). These patients did not have the usual clinical clues to suggest RAS. High-grade bilateral renal artery disease was present in approximately 13% of the patients. In the 319 patients reported in 6 different studies, 44% had bilateral RAS (8). Other studies have shown that 22–59% of patients with peripheral arterial disease have significant RAS (21).

It has also been established that RAS is common in patients with coronary artery disease. Of 7,758 patients undergoing cardiac catheterization during a 78-month period, 3,987 underwent aortography to screen for RAS at the time of catheterization (22). One hundred ninety-one (4.8%) subjects had greater than 75% stenosis of the renal artery. Severe bilateral disease occurred in 0.8%. In the Mayo Clinic series (23), renal arteries were studied at the time of cardiac catheterization in patients with hypertension. Ninety percent of the renal arteries were adequately visualized and no complications occurred from the aortogram. Greater than 50% stenosis of the renal artery was present in 19.2%. Greater than 70% stenosis occurred in 7%. Bilateral RAS was present in 3.7% of patients.

Natural History

Knowledge of the natural history is extremely important in the subsequent management of patients with RAS. Most natural history studies reported in the literature were retrospective studies. The rates of progression ranged from 36–71% (24). In Schreiber's series (24), only 16% of patients progressed to total occlusion over a mean follow-up of 52 months. However, the rate of progression to total occlusion occurred more frequently (39%) when there was a stenosis greater than 75% on the initial renal arteriogram.

Zierler et al. (25) utilized renal duplex ultrasound to prospectively study anatomic progression of atherosclerotic renovascular disease. If the renal arteries were normal, only 8% progressed over a 36-month period. However, at 3 years, 48% of patients progressed from less than 60% stenosis to 60% or greater stenosis. All four renal arteries that progressed to occlusion had greater than 60% stenosis at the initial visit. Progression of RAS occurred at an average rate of 7% per year for all categories of baseline disease combined.

The effect of RAS on kidney size has been well studied (26). Using duplex ultrasound, Caps and colleagues prospectively followed 204 kidneys in 122 patients with known renal artery stenosis for a mean of 33 months. The cumulative incidence of renal atrophy was 5.5% in those kidneys considered to have no renal artery disease, while renal atrophy occurred in those kidneys in which the RAS was less than 60%. Renal atrophy occurred in 20.8% of those kidneys in which the RAS exceeded 60% ($p=0.009$, log rank test).

There are no good data to assess the prevalence of end-stage renal disease (ESRD) caused by renal artery stenosis. Scoble et al. (27) found

TABLE 1

Prevalence of Atherosclerotic Renal Artery Stenosis

> 50% stenosis	Abdominal Aortic Aneurysm (n=109)	Aortoiliac Occlusive Disease (n=21)	Peripheral Arterial Disease (n=189)	Renal Artery Stenosis (n=76)
All patients	41 (38%)	7 (33%)	74 (39%)	53 (70%)*
Diabetic patients	6 (50%)	1 (33%)	34 (50%)**	10 (71%)
Nondiabetic patients	35 (36%)	6 (33%)	40 (33%)	43 (69%)

** $p<0.001$
** $p<0.02$

Reproduced with permission from Olin JW, Melia M, Young JR, et al. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. Am J Med 1990; 88:46N–51N (1).

that atherosclerotic renovascular disease was the cause of ESRD in 14% of patients starting dialysis therapy. Mailloux and colleagues (28) reviewed the causes of ESRD in 683 patients over a 20-year period. Eighty-three patients (12%) had documented RAS as a cause of ESRD. Patients receiving dialysis due to renal artery disease had a much poorer prognosis than patients with ESRD due to other causes (Table 2) (28).

The mere presence of RAS, even prior to developing ESRD, portends a poor prognosis. Patient survival decreases as the severity of RAS increases, with 2-year survival rates of 96% for patients with unilateral RAS, 74% for patients with bilateral RAS, and 47% in patients with stenosis or occlusion to a solitary functioning kidney (29).

Clues to the Diagnosis of Renal Artery Stenosis

Most patients with atherosclerotic RAS have one or more of the clinical clues listed in Table 3.

Individuals who develop hypertension between the ages of 30 and 55 usually have primary (essential) hypertension. If the initial diagnosis of hypertension is made before the age of 30, it may be due to FMD. Since atherosclerosis occurs in older individuals, it is usually the cause of RAS after the age of 55. Accelerated or malignant hypertension has also been associated with a very high prevalence of RAS. "Resistant hypertension" is defined as failure to normalize blood pressure to less than 140/90 mm Hg (30) following a trial consisting of at least three drugs with different mechanisms of action. The diagnosis of renovascular disease should be strongly considered in patients with resistant hypertension.

Gifford et al. (31) found that 71% of patients (53 of 75 patients) with an atrophic kidney had severe stenosis or complete occlusion of the renal artery ipsilateral to the small kidney. Three studies have shown that if there is a discrepancy in size between the two kidneys or if one kidney is atrophic, there is a 60% chance that the contralateral renal artery (normal-sized kidney) is severely stenotic (9). Therefore, the presence of an atrophic kidney or a discrepancy in size between the two kidneys demands a thorough investigation for the presence of renovascular disease. Likewise, patients who develop azotemia while receiving an ACE inhibitor or ARB should be investigated for the presence of RAS (13–16).

Recurrent CHF and "flash" pulmonary edema not related to active ischemic heart disease can result from bilateral RAS (or unilateral RAS to a single functioning kidney). This is probably related to undue volume expansion. The use of ACEI or ARB by these patients with high-grade bilateral disease may be contraindicated (9).

TABLE 3

Clinical Clues to the Diagnosis of Atherosclerotic Renal Artery Stenosis

- Onset of hypertension after the age of 55
- Exacerbation of previously well-controlled hypertension
- Malignant hypertension
- Resistant hypertension
- Epigastric bruit (systolic/diastolic)
- Unexplained azotemia
- Azotemia while receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blocking agents
- Atrophic kidney or discrepancy in size between the two kidneys
- Recurrent congestive heart failure or "flash" pulmonary edema
- Atherosclerosis elsewhere

TABLE 2

Survival Estimates for Selected Renal Diagnoses on Dialysis

Diagnosis	Median Survival	Length of Survival			
		2 year	5 year	10 year	15 year
Polycystic kidney disease (n=56)	133 months	91%	77%	59%	32%
Malignant hypertension (n=23)	55 months	77%	25%	0	0
Renal vascular disease (n=83)	25 months	56%	18%	5%	0

Reproduced with permission from Mailloux LU, Napolitano B, Bellucci AG, et al. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. Am J Kidney Dis 1994; 24:622–629 (28).

Diagnosis of Renovascular Disease

The ideal imaging procedure for RAS should: (a) identify the main renal arteries as well as accessory vessels; (b) localize the site of stenosis or disease; (c) provide evidence for the hemodynamic significance of the lesion; and (d) identify associated pathology (e.g., abdominal aortic aneurysm, renal mass, etc.) that may have an impact on the treatment of the renal artery disease (32, 33).

Angiography, once considered the "gold standard" for arterial imaging, is rarely required to make the diagnosis of RAS. Usually one or more of the noninvasive modalities can accurately assess the renal arteries. Exceptions to this general rule may occur in patients with FMD or renal artery aneurysms, where there may be branch involvement. Pressure gradients should also be obtained, to confirm the physiological significance of a given lesion. CO_2 and gadolinium angiography are non-nephrotoxic contrast agents that may be particularly useful in patients with renal insufficiency.

Renal Arteriography at the Time of Cardiac Catheterization

Since RAS is common in patients with coronary artery disease, some cardiologists perform an aortogram on the "way out" after performing a cardiac catheterization (2, 34). This is a hotly debated issue at the present time. We should have some guidance of the advisability of renal angiography at the time of cardiac catheterization when the ACC/AHA Guidelines for the Management of Patients with Peripheral (and renal) Arterial Disease are published within the next year. If the patient meets clinical criteria for intervention (see below) it is advisable to perform an abdominal aortogram at the time of the catheterization. We are opposed to the stenting of an RAS just because a stenosis is found (35).

Duplex Ultrasonography

Duplex ultrasonography is an excellent test for detecting RAS (Fig. 1). It is the least expensive of the imaging modalities and provides useful information about the degree of stenosis, the kidney size, and other associated disease processes such as aneurysms or obstruction. Duplex may also help predict which patients will demonstrate an improvement in blood pressure control or renal function after renal artery angioplasty and stenting (36).

Duplex ultrasonography combines B-mode ultrasound and Doppler examination. In the longitudinal (long axis) view, the peak systolic flow velocity in the aorta is recorded at the level of the renal arteries. The aortic velocity and the highest renal artery peak systolic velocity are used to calculate the renal aortic ratio. This technique is discussed in detail in several reviews (9, 32, 37). Overall, when compared to angiography, duplex ultrasound has a sensitivity and specificity of 84–98% and 62–99% respectively when used to diagnose RAS (32). We performed a prospective study comparing duplex ultrasound to angiography (Table 4) (37). If the end diastolic velocity was greater than 150 cm/sec, then the degree of stenosis was likely to be greater than 80%.

It is very important to measure the resistive index during the renal artery duplex examination. A Doppler waveform is obtained from the parenchyma of the kidney. The resistive index is calculated by the formula:

$$\frac{\text{PSV} - \text{EDV}}{\text{PSV}}$$

where PSV = peak systolic velocity
and EDV = end diastolic velocity

A recent study used Doppler ultrasonography to predict the outcome of therapy in patients with RAS (36), 97% of patients with resistance index greater than 80 demonstrated no improvement in blood pressure and 80% had no improvement in renal function. The authors suggest that the increased resistive index is an indication of structural abnormalities in the small blood vessels of the kidney. Such small vessel disease has been seen with longstanding hypertension associated with nephrosclerosis or glomerulosclerosis. If these results are confirmed, it could provide a method for predicting which patients will improve after percutaneous intervention.

Renal artery duplex is an excellent test for the follow-up of RAS after percutaneous therapy or surgical bypass (Fig. 1C). Unlike magnetic resonance angiography (which may be affected by artifact or scatter produced by the stent), ultrasound transmission through the stent is not a problem.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) provides excellent imaging of the abdominal vasculature and associated anatomical struc-

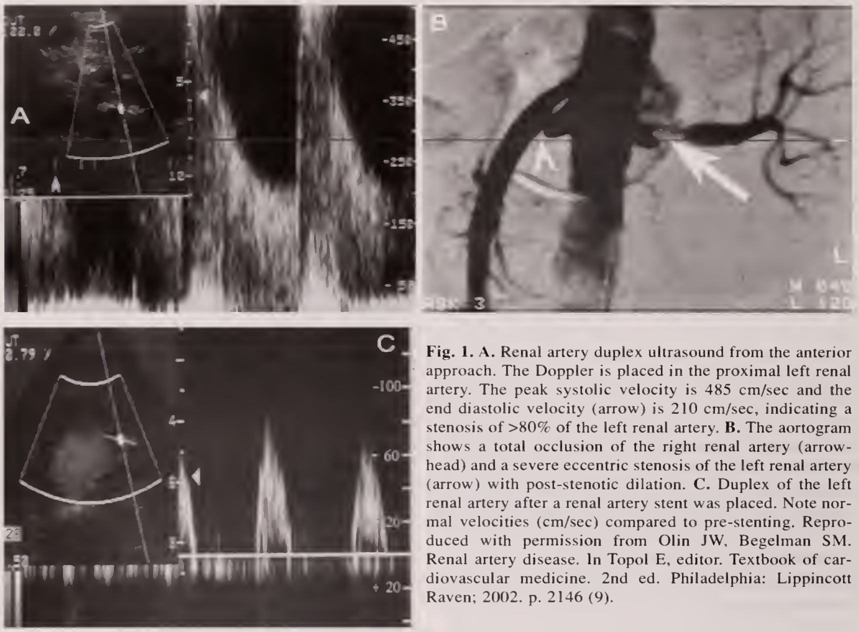


Fig. 1. A. Renal artery duplex ultrasound from the anterior approach. The Doppler is placed in the proximal left renal artery. The peak systolic velocity is 485 cm/sec and the end diastolic velocity (arrow) is 210 cm/sec, indicating a stenosis of >80% of the left renal artery. **B.** The aortogram shows a total occlusion of the right renal artery (arrowhead) and a severe eccentric stenosis of the left renal artery (arrow) with post-stenotic dilation. **C.** Duplex of the left renal artery after a renal artery stent was placed. Note normal velocities (cm/sec) compared to pre-stenting. Reproduced with permission from Olin JW, Begelman SM. Renal artery disease. In Topol E, editor. Textbook of cardiovascular medicine. 2nd ed. Philadelphia: Lippincott Raven; 2002. p. 2146 (9).

TABLE 4

Comparison of Duplex Ultrasound with Arteriography

Stenosis by Ultrasound	Stenosis by Arteriography				
	0–59%	60–79%	80–99%	100%	Total
0–59%	62	0	1	1	64
60–99%	1	31	67	0	99
100%	0	1	1	22	24
Total	63	32	69	23	187

Sensitivity	0.98
Specificity	0.98
Positive predictive value	0.99
Negative predictive value	0.97

Reproduced with permission from Olin JW, Piedmonte MR, Young JR, et al. The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. Ann Intern Med 1995; 122:833–838 (37).

tures. Contrast-enhanced MRA provides a superior quality study when compared to noncontrast studies. Gadolinium chelate is the contrast agent of choice, but other contrast agents, which are under development, may improve the current imaging techniques. Unlike ionic and non-ionic iodinated contrast agents, gadolinium is not nephrotoxic and can be used safely in patients with renal insufficiency. The imaging time is substantially shortened, and 20–40 second acquisition times are not uncommon. This eliminates some artifact created by gross patient movement (32, 38). When compared to angiography, MRA has demonstrated a sensitivity of

90–100% and a specificity of 76–94% (32, 38–40). A recent meta-analysis was performed with 499 patients who underwent a gadolinium-enhanced MRA and catheter angiography within 3 months of one another. The sensitivity and specificity of MRA were 97% and 93% respectively. MRA accurately identified accessory renal arteries 82% of the time (41). However, MRA does not have the same sensitivity and specificity for patients with FMD.

CT Angiography

Computed tomography (CT) angiography is another strategy for the diagnosis of RAS. The sensitivity and specificity are good; however, it requires a large bolus of contrast, thus making it a less attractive diagnostic strategy in the azotemic patient. However, with the advent of multi-detector 16 row CT scanners, one can get clearer images in a shorter period of time and with less contrast. This technique is gaining in popularity for the evaluation of renal artery stenosis.

Captopril Renography

Radionuclide imaging techniques provide a noninvasive and safe way to evaluate renal blood flow and excretory function. When an ACE inhibitor such as captopril is added to isotope renography, the sensitivity and specificity of the test improve considerably, especially for patients with unilateral RAS. In most instances of unilateral RAS, the glomerular filtration rate of the stenotic kidney falls by approximately 30% after captopril administration (42). In contrast, the contralateral normal kidney exhibits an increase in glomerular filtration rate, urine flow and salt excretion despite a reduction in systemic blood pressure. These expected physiologic changes within the stenotic and contralateral kidneys are the basis of the asymmetry of renal function following ACE inhibition detected by renal scintigraphy.

Overall, the accuracy of captopril renography in identifying patients with renovascular disease appears quite acceptable, with a sensitivity of about 85–90% (range 45–94) and specificity of about 93–98% (range 81–100). Those patients with unilateral disease and normal renal function would be best suited for a captopril renogram. The presence of significant azotemia or bilateral RAS may adversely affect the accuracy of captopril renography. Many investigators have excluded patients with serum creatinine exceeding 2.5–3.0 mg/dL.

While the captopril renogram was once the noninvasive diagnostic test of choice for patients with RAS, it is now relegated to a secondary screening modality, since the quality of the images of duplex ultrasound, MRA, and CT angiography are so good.

Renal Vein Renin

Renal vein renin measurement is not a useful test to screen for RAS (9). In addition, it rarely adds value in determining who will benefit from therapy. Except under unusual circumstances, we do not use this as a diagnostic test. One useful diagnostic algorithm is shown in Fig. 2 (43).

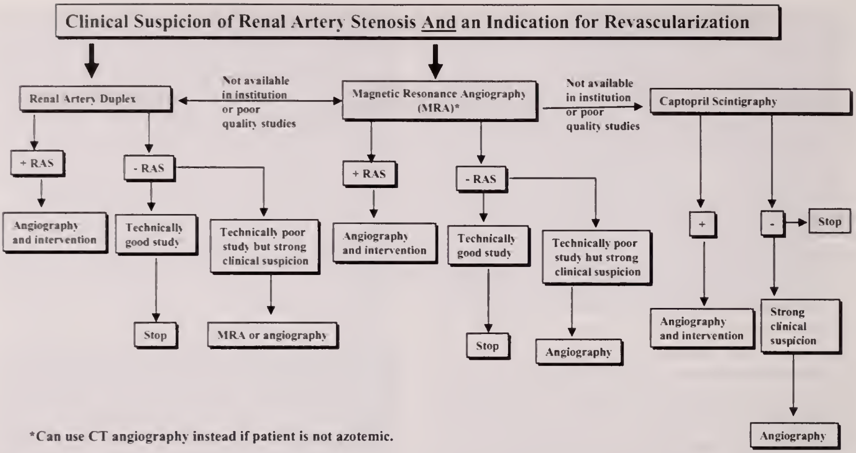
Management of Renal Artery Disease

Prior to 1990, if a patient met the criteria for intervention, surgical renal artery revascularization was usually performed. However, since the introduction of stents, surgical revascularization is rarely performed solely for the treatment of renal artery disease. Despite advances in the technical aspects of angioplasty and stent implantation, there is a paucity of controlled clinical trials assessing the role of renal artery angioplasty and stenting to control hypertension or to preserve renal function. Controversy still exists as to the value of renal artery stenting and the appropriate indications for this procedure. The indications for PTA/stent implantation for atherosclerotic RAS include at least a 70% stenosis of one or both renal arteries and at least one of the following:

- Inability to adequately control the blood pressure despite a good antihypertensive regimen.
- Chronic renal insufficiency not related to another clear-cut cause (disease should be bilateral or stenosis to a solitary functioning kidney). The treatment of an elevated serum creatinine with unilateral disease is controversial, and there are no good clinical trials to help guide the clinician (44).
- Dialysis-dependent renal failure in a patient without another definite cause of ESRD (45–47).
- Recurrent CHF or "flash" pulmonary edema not attributable to active ischemia (10, 48–50).

Medical Therapy

All patients with hypertension should be treated medically, even if they undergo other


Clinical Suspicion of Renal Artery Stenosis And an Indication for Revascularization
Renal Artery Duplex
Not available in institution or poor quality studies
Magnetic Resonance Angiography (MRA)*
Not available in institution or poor quality studies
Captopril Scintigraphy
+ RAS
- RAS
+ RAS
- RAS
Angiography and intervention
Technically good study
Technically poor study but strong clinical suspicion
Angiography and intervention
Technically good study
Technically poor study but strong clinical suspicion
+
-
Stop
Stop
MRA or angiography
Stop
Angiography
Angiography and intervention
Strong clinical suspicion
Angiography

*Can use CT angiography instead if patient is not azotemic.

Fig. 2. Algorithm for the diagnosis of renal artery stenosis. Adapted with permission from Carman T, Olin JW. Diagnosis of renal artery stenosis: what is the optimal diagnostic test? Curr Interv Cardiol Rep 2000; 2:116 (43).

types of intervention. A comprehensive risk factor reduction program should be undertaken. Antiplatelet agents should be prescribed to help lower the extremely high cardiovascular morbidity and mortality that occurs in this patient population. Many patients have superimposed essential hypertension and will still require lifelong antihypertensive therapy even after revascularization of the renal arteries.

Patients with RAS who are treated solely with medical therapy should be carefully followed for progression of disease. Renal function should be evaluated every three months, along with periodic serial duplex ultrasound imaging.

Percutaneous Transluminal Angioplasty

Percutaneous transluminal angioplasty (PTA) is the treatment of choice for patients with FMD. However, since most patients with atherosclerotic RAS have ostial or proximal disease, the preferred endovascular therapy utilizes stent implantation. While blood pressure control and preservation of renal function may occur, the restenosis rate is extraordinarily high with angioplasty alone (51).

There have been three randomized prospective trials comparing medical management to angioplasty for blood pressure control in patients with atherosclerotic RAS (52–54). Each of the three studies has significant drawbacks precluding any definite conclusions. In the prospective study published by van Jaarsveld et al. (54), 106 patients with angiographically documented RAS were randomly assigned to PTA or medical therapy, and had blood pressure and renal function assessed at 3 and 12 months. Baseline blood pressure was 179/104 mm Hg and 180/103 mm Hg in the angioplasty and drug therapy groups respectively. At 3 and 12 months, there was no significant difference in the degree to which blood pressure was controlled between the two groups, but the extent and dose of antihypertensive medications was lowered in the PTA group. Unfortunately, there were several rather serious problems that make interpretation of the results difficult (55). For example, 44% of patients randomized to medical therapy crossed over to the balloon angioplasty group, resulting in dilution of the long-term outcome differences. In addition, there was a favorable trend to all primary outcome events, and with the small sample size, we calculated that the chance of a type II statistical error was substantial. Finally, the authors chose a 50% diameter reduction as the cut-off for "hemodynamically significant" renal artery lesions, despite the clear evidence that a lesion of at least 70% stenosis is required to cause significant hypertension or a decrement in renal function (3). Only 57% of the patients had stenosis of greater than 70%.

Renal Artery Stents

Due to the high restenosis rate with angioplasty alone, endovascular stents offer a significant advantage over PTA in patients with atherosclerotic disease, especially those with ostial stenosis. The degree of stenosis after stenting approaches zero, and most dissection flaps caused by PTA alone are successfully sealed with stents (Fig. 3) (9). However, despite the widespread use of stents in thousands of renal arteries since the late 1980s, there is still no Food and Drug Administration approval of these devices for the renal circulation.

For the best results, the shortest stent to adequately cover the lesion should be used. The stent must extend 1 – 2 mm into the aorta in patients with ostial disease and be fully expanded. Underdeployment of the stent is a common problem early in an operator's experience. It may be worthwhile to do the first several cases with intravascular ultrasound, to be certain the stent is adequately expanded. It is also important to make sure that no post-procedure pressure gradient exists.

White, Ramee and associates (56) evaluated the safety and efficacy of renal artery stent implantation in patients with lesions that did not respond well to angioplasty alone. Balloon expandable stents were placed in 100 consecutive patients (133 renal arteries). The technical success of the procedure was 99%. The mean blood pressure values were 173±25/88±17 mm Hg prior to stent implantation and 146±20/77±12 mm Hg six months after renal artery stenting ($p<0.01$). Angiographic follow-up with 67 patients (mean 8.7±5 months) demonstrated restenosis (RAS had exceeded 50%) in 15 patients (19%).

Blum et al. (6) prospectively placed a Palmaz stent in 68 patients (74 lesions) with ostial RAS and suboptimal PTA. Five-year patency was 84.5% (mean follow-up was 27 months). Restenosis occurred in 8 of 74 arteries (11%), but after reintervention the secondary 5-year patency rate was 92.4%. Blood pressure was cured or improved in 78% of patients. There was no significant change in the serum creatinine values after stent implantation.

A meta-analysis of 14 studies (678 patients) compared the technical success, clinical efficacy and restenosis rate after PTA and stent implantation (Table 5) (57).

The effect that renal artery stent implantation had on preserving renal function was studied in 2 small series (58, 59). Both studies used the reciprocal of the serum creatinine to determine the rate of decline or improvement in renal function. Harden et al. (58) placed renal artery stents in 32 patients (33 arteries) and reported that renal function improved or stabilized in 22 patients (69%). In 25 patients with complete follow-up, Watson and associates (59) demonstrated that after stent placement, the slopes of the reciprocal of the serum creatinine (1/Scr) were positive in 18 patients and less negative in 7 patients.

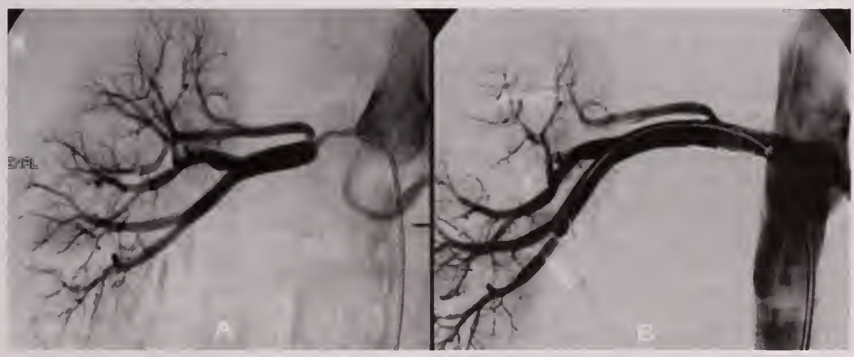


Fig. 3. A. Severe stenosis of the right renal artery beginning at its ostium and extending distally to a branch that supplies the upper pole of the kidney. **B.** Excellent angiographic result after stent placement. The smaller superior branch is still patent despite being covered by the stent (stent jail). Courtesy of J. Michael Bacharach, M.D., M.P.H. Reproduced with permission from Olin JW, Begelman SM. Renal artery disease. In: Topol E, editor. Textbook of cardiovascular medicine. 2nd ed. Philadelphia: Lippincott Raven; 2002. pp. 2149 (9).

TABLE 5

Clinical and Angiographic Follow-up in Patients Who Underwent Renal Artery Stent Placement

Study	No. Pts	Stent	Technical Success	Follow-up (months)	Hypertension		Renal Function		Restenosis	Complications
					Cure	Improved	Improved	Stable		
Wilms	11	Wallstent	83%	7	30%	40%	0%	0%	29%	3 (25%)
Kuhn	10	Strecker	80%	11	29%	43%	50%	NM	25%	4 (40%)
Ree	28	Palmaz	96%	7	11%	54%	36%	36%	39%	5 (18%)
Hennequin	21	Wallstent	100%	32	14%	86%	17%	50%	20%	4 (19%)
van de Ven	24	Palmaz	100%	6	68%	5%	36%	64%	13%	3 (11%)
Henry	59	Palmaz	100%	14	19%	57%	20%	NM	9%	2 (3%)
Iannone	63	Palmaz	99%	10	4%	35%	36%	45%	14%	11 (13%)
Blum	68	Palmaz	100%	27	16%	62%	NM	NM	11%	0 (0%)
Bosclair	33	Palmaz	100%	13	6%	61%	41%	35%	—	6 (17%)
Harden	32	Palmaz	100%	6	NM	NM	34%	34%	13%	1 (3%)
White	100	Palmaz	99%	6	NM	NM	20%	NM	19%	2 (2%)
Rundback	45	Palmaz	94%	17	NM	NM	NM	NM	25%	5 (9%)
Shannon	21	Palmaz	100%	9	NM	NM	43%	29%	0%	2 (9%)
Dorros	163	Palmaz	100%	48	3%	51%	NM	NM	—	23 (11%)
Total	678	...	98%*	16*	20%*	49%*	30%	38%	17%	11*

*Mean based on random-effects model

Reproduced with permission from Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. Radiology 2000; 216:78–85 (57).

Complications of renal artery stent placement include access-related complications such as hematoma, retroperitoneal hemorrhage, pseudoaneurysm, arterio-venous fistula, vessel occlusion, and infection. However, the most serious complications result from atheromatous embolization to the kidneys, bowel and legs. Stent malposition and rupture of the renal artery are less common complications. The complication rate varies considerably between centers. High volume centers generally can perform renal artery stenting with minimal morbidity and mortality. Although all studies reported use of an antithrombotic agent during the procedure and most patients were discharged on an antiplatelet agent, the regimens varied.

There has been preliminary experience with emboli protection devices in Europe; clinical trials are just getting underway in the United States. When these devices are used, a wire is placed across the renal artery lesion and a balloon occlusion device or a filter device is deployed in the distal renal artery. The purpose of this is to capture the atherosclerotic debris caused by angioplasty and stenting, with a goal of preventing atheromatous embolization to the kidneys. Henry et al. used the PercuSurge™ GuardWire device on 32 arteries in 28 patients (60). The procedure was technically successful in all patients, and visible debris was recovered in all patients. Protected renal artery stenting is an exciting area for investigation to determine its efficacy.

Surgical Revascularization

Surgical revascularization plays a much smaller role than it had previously, due to the excellent technical results achievable with angioplasty and stent implantation. Many patients can now undergo renal artery stent implantation as an outpatient procedure, at a fraction of the cost of surgical revascularization.

Current indications for surgical revascularization include: branch disease from FMD that cannot be treated adequately with balloon angioplasty (4); recurrent stenosis after stenting (however, this has been extremely rare in our experience) (9); or simultaneous aortic surgery (abdominal aortic aneurysm repair or symptomatic aortoiliac disease). Even in this last circumstance, it may be advisable to stent the renal artery first and then proceed with aortic reconstruction. The mortality rate of aortic replacement and renal artery revascularization is higher than for either procedure alone (61).

The Role of Revascularization for Renal Salvage

Patients who are at a markedly increased risk of renal failure are those with greater than 70% bilateral RAS or severe stenosis to a single functioning kidney. In this patient subgroup, the risk of total occlusion of the renal artery is significant, and if this occurs, the outcome is a critical decrease in functioning renal mass, with resulting renal failure (4, 45–47, 62–64).

Complete occlusion of the renal artery most often results in irreversible ischemic damage to the involved kidney. However, in some patients with gradual arterial occlusion, the viability of the kidney can be maintained through the development of collateral arterial supply (62, 64). There are certain clues that may help to predict renal salvageability in patients with an occluded renal artery:

- Angiographic demonstration of late filling of the distal renal arterial tree by collateral vessels on the side of total arterial occlusion (64)
- Renal size of 8–9 cm
- Function of the involved kidney on a renal flow scan
- The presence of a nephrogram after a contrast arteriogram
- A renal biopsy showing well-preserved glomeruli and an absence of significant glomerulosclerosis

There are reports showing that restoration of renal function in patients with totally occluded renal arteries is feasible with either endovascular therapy or surgical revascularization. Kaylor et al. (46) reported on 9 patients who were on dialysis secondary to atherosclerotic RAS for between one week and 13 months. Reversal of end-stage renal failure occurred in all 9 patients with surgical revascularization. The serum creatinine at one month ranged from 1.1–4.2 mg/dL (mean 2.5 mg/dL). Hansen and colleagues (47) have also shown that it is possible to restore renal function with surgical revascularization in some patients who have been on chronic hemodialysis therapy. From 1987–1993, 340 patients underwent surgical renal revascularization. Twenty patients were receiving hemodialysis before renal artery repair. Hemodialysis was discontinued in 16 of the 20 patients (80%). Two of the 16 patients resumed dialysis 4 and 6 months after surgery. The long-term survival was better for those who were dialysis independent than for those who required ongoing dialysis therapy. There were only 2 late deaths among the 14 patients not receiving dialysis, compared to 5 late deaths among the 6 patients who continued to receive dialysis after surgical revascularization ($p<0.01$).

The likelihood of improving renal function appears to be dependent on a relationship between the severity of stenosis of the main renal artery, the rapidity in the development of renal failure and the degree of parenchymal damage to the kidney. Several investigators have suggested that parenchyma damage may in fact be the most important determinant of non-reversibility of renal failure (12).

Revascularization for Control of Congestive Heart Failure or Flash Pulmonary Edema

The emerging indications for renal revascularization are CHF and flash pulmonary edema (10, 49, 65–67). Patients with these conditions most often have significant bilateral RAS or RAS to a solitary functioning kidney. The left ventricular systolic function may be normal or impaired and the blood pressure may be well controlled (10). We reported 39 patients who underwent renal artery stent implantation for control of CHF (10). This represented 19% of our renal artery stent population. In this series, 18 patients (46%) had bilateral RAS and 21 patients (54%) had stenosis to a solitary functioning kidney. Renal artery stent implantation was technically successful in all 39 patients. The blood pressure was improved in 72% of the patients. Renal function was improved in 51%, remained stable in 26% and deteriorated in 23%. The mean number of hospitalizations for CHF prior to stenting was 2.37 ± 1.42 (range 1–6); after stenting it was 0.30 ± 0.065 (range 0–3), $p<0.001$. Seventy-seven percent of the patients had no further hospitalizations after renal artery stenting, over a mean follow-up period of 21.3 months.

The mechanism by which RAS causes CHF and pulmonary edema is not well defined. The improvement after stenting may in part be related to the ability to use ACEIs, especially for those with impaired left ventricle function and the ability to better control volume.

The Future

Over the last decade, renal artery angioplasty and stenting has become much safer because of better equipment and more experienced operators. There are several important questions that need to be answered in the upcoming years:

- How can we more accurately predict which patients will respond favorably after revascularization and which patients will not?
- Will emboli protection devices prevent the worsening in renal function that occurs in some patients after renal intervention?

- Will drug eluting stents prevent restenosis in the 15 – 20% of patients who demonstrate evidence of restenosis?
- Why is the survival rate so poor for patients who have atherosclerotic renal artery stenosis? Will renal revascularization improve the survival rate? Will a more comprehensive risk factor reduction strategy lower mortality?
- What is the mechanism of CHF in patients with bilateral disease or disease in a single functioning kidney?

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Induction of Immunity against Human Cytomegalovirus

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Abstract

Most healthy individuals have been exposed to human cytomegalovirus (HCMV) and harbor the virus in a dormant form. However, in situations of immune compromise, HCMV infection is associated with high mortality rates in recipients of bone marrow transplants and with significant morbidity in recipients of solid organ transplants. Conventional vaccination with attenuated HCMV or HCMV proteins fails to prime protective immune responses, presumably because the antigens fail to be presented effectively *in vivo*. Dendritic cells (DC) are professional antigen-presenting cells that can be genetically engineered to direct their ability to induce immune responses toward immunodominant HCMV antigens. DC are a distinct lineage of leukocytes whose function is most notable for their ability to form clusters with T cells and stimulate vigorous cytotoxic T lymphocyte responses. We hypothesize that in this capacity, DC engineered to express HCMV antigens are uniquely positioned to control immunity against HCMV.

Key Words: Cytomegalovirus, vaccine, immunity, gene transduction, dendritic cells.

Background

Clinical Human Cytomegalovirus Infection and Immunity

HUMAN CYTOMEGALOVIRUS (HCMV) is the largest member of the human herpesvirus family. By school age, almost all individuals (>90%) have been exposed to HCMV and have developed protective immunity, but a lifelong latent and asymptomatic infection is established with periodic reactivation and viral shedding at mucosal sites. However, symptomatic reactivation of latent HCMV infection is common in immune-compromised patients and results in severe infections. The incidence of HCMV infection in the first 100 days following allogeneic bone marrow transplantation (BMT) ranges from 30–70% (1–4). In the past, HCMV has been the leading infectious cause of death in BMT recipients, with mortality rates of untreated HCMV pneumonia of 30–60% (1, 5). Significant HCMV morbidity is also frequently associated with solid (kidney, liver, heart) organ transplantation (6–8). In addition, it has been estimated that each year approximately 40,000 newborns in the U.S. are infected prenatally with HCMV and that up to 7,000 of these newborns develop permanent central nervous system damage as a result of the infection (9). Conventional vaccination with attenuated HCMV or HCMV proteins fails to prime protective immune responses, and the standard therapy at present is treatment with ganciclovir, but at a substantial financial cost. Although ganciclovir prophylaxis reduces the incidence of HCMV disease early after organ transplantation, severe neutropenia occurs in 30% of patients and there is an increased incidence of HCMV disease of late onset (>100 days) (10, 11).

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The fundamental role of a competent T lymphocyte response for resolution of acute HCMV infection is supported by the occurrence of progressive infections in individuals with acquired T cell deficiencies. Conversely, after bone marrow transplantation, recovery from HCMV infection correlates with recurrence of antiviral cytotoxic T lymphocyte (CTL) responses. Adoptive transfer of CD8$^+$ T cells derived from the bone marrow donors reconstitutes cellular immunity to HCMV (12, 13). Studies in humans, using target cells infected with laboratory strains or primary patient isolates of HCMV, have analyzed epitopes recognized by CTLs. Epitopes recognized by the immunodominant CD8$^+$ CTL clones are conserved in all tested strains, suggesting that genetic heterogeneity of the virus is unlikely to present a significant obstacle to successful cell-mediated immunotherapy (14). CD4$^+$ T helper cell functions are required for persistence of the CD8$^+$ CTL response (13, 15). The major role of CD4$^+$ T cells is production of cytokines which assists in the direction of immune responses toward either predominant-cell-mediated type 1 (Th1) or antibody-mediated type 2 (Th2) responses.

Although cellular immunity in transplant patients correlates with recovery from primary infection (12, 16), humoral immunity probably plays a role in limiting the infection, both by clearing the virus load (17, 18) and by protecting against subsequent viral reactivation (19, 20). However, in several studies with solid organ and BMT recipients, the protective effect of HCMV-specific immunoglobulin has been difficult to demonstrate and is controversial (21).

Immune Responses Against HCMV Antigens

HCMV contains a 240 kb double-stranded DNA genome with more than 200 open reading frames, the products of only a minority of which have been experimentally characterized (22–25). Although the virion contains more than 30 proteins, with molecular weights ranging from 20–200 kDa, the CTL response against HCMV is limited to a few proteins, with the predominant response directed against the pp65 tegumentum protein. Other components of the virion proteins (pp150, pp28), immediate-early (IE1 and IE2) antigens and the DNA-binding protein (pp52) have been suggested to be targets for CTLs, but at much lower frequencies (26–28).

The pp65 is the major viral tegumentum protein and is produced predominantly during the late phase of gene expression (29). The pp65 protein is a phosphoprotein which constitutes 18% of the virion protein mass, but is dispensable for HCMV replication (30). It is transferred into cells with the HCMV virion at the onset of infection, prior to viral gene expression, suggesting that immunity to viral antigens may be targeted, in part, to structural proteins which do not require *de novo* gene expression (22, 31).

The pp65 antigen is the most extensively studied antigenic target for major histocompatibility complex (MHC) class I restricted CTLs (22, 27, 28, 32–34). Seventy to ninety percent of all CTLs against HCMV have been shown to be specific for pp65 (33). Analysis of the peptide specificity of the pp65-specific CTLs has shown that responses to individual peptide sequences are shared among most human histocompatibility leukocyte antigen (HLA)-A2 seropositive donors, but that for some subjects multiple peptides are recognized throughout the pp65 protein (33). A high level of pp65-specific CTL is maintained over a prolonged period (18–20 months), which may reflect a continued expression of pp65. This supports the idea that periodic reactivation or chronic low level replication of the virus allows for restimulation and maintenance of the CTL memory pool (33). This observation is different from that of other viral infections, such as influenza, in which the CTL response progressively declines over time (35). Therefore, it is conceivable that the demonstrated variations in peptide specificities seen in HCMV-seropositive donors are a result of progressive selection or broadening of the CTL response in favor of particular peptide-HLA class-I associations that control a persistent but latent infection. Thus, a broadened CTL response may be beneficial for obtaining a more sustained effect of vaccination against HCMV, and suggests that designs to stimulate broader CTL responses should be investigated. Furthermore, studies of the fine specificity of the pp65 CTL response from HLA-A2 donors and HLA-A2 transgenic mice have revealed that a common region of the protein (aa 393–507) is recognized in transgenic mice and humans (28, 33). This result suggests that an HLA-A2 transgenic mouse model can be used to study vaccine development, because the obtained CTL responses in transgenic mice, in most cases, are predictive for human CTL responses (28, 36).

Immune Evasion by HCMV

HCMV can evade the immune response directed against viral proteins expressed during the replication cycle. It appears that many genes expressed by HCMV may act in concert to provide an "immune privileged" site for HCMV replication (Table) (37–49). These mechanisms of immune evasion may explain why CTL responses against the pp65 tegument antigen, which does not require *de novo* synthesis, predominate compared to responses to viral antigens produced during the replication cycle when the viral countermeasures are in place.

Results

To induce the expression of HCMV antigens in primary antigen-presenting dendritic cells (DC), we have developed adenoviral recombinants (Adpp65 and Adpp150) expressing pp65 and pp150 antigens. These recombinants were tested by transient expression in transfected cell lines. Fig. 1 shows HCMV pp65 protein expression after transfection of the Ad-HCMVpp65 plasmid into QT6 cells and immunoprecipitated with pp65-specific antibody. The sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) revealed abundant expression of pp65 in the two transfected cell cultures (lanes 3 and 4) and compared to untransfected control cells (lane 1). Comparable results were obtained with the AdHCMVpp150 plasmid (not shown).

The adenoviral Adpp65 recombinant was next tested in primary cells (Fig. 2) (50). The

TABLE

Immune Evasion Induced by HCMV Genes

Function	HCMV Gene	References
Downregulation of MHC class I a) Degradation of heavy chains b) Retention of heavy chains in ER c) Translocation of peptide in ER	US2, US3, US6 US11	(37–40)
Chemokine trapping		
a) chemokine receptor	US27, US28	(41, 42)
Chemokine homologs	UL146	(43)
TNF receptor	UL144	(44)
IL-10 homolog	UL11a	(45, 46)
IL-10 induction (murine)		
NK cell evasion		
a) MHC homolog	UL36	(47, 48)
Apoptosis inhibitors	UL36	(49)

HCMV = human cytomegalovirus; MHC = major histocompatibility complex; ER = endoplasmic reticulum; TNF = tumor necrosis factor; IL-10 = interleukin-10; NK = natural killer

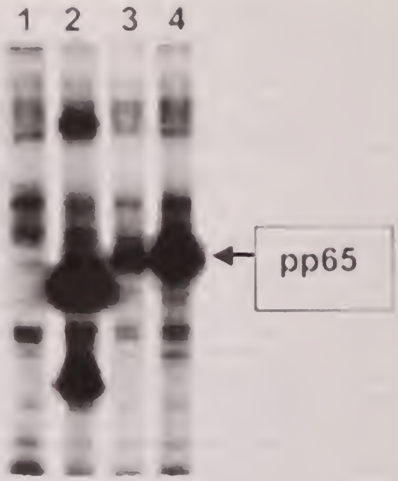

Fig. 1. Autoradiogram of sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showing pp65 expression in QT6 cells after immunoprecipitation with specific antibodies and SDS-PAGE. **Lane 1**: Negative control — untransfected control cells precipitated with anti-pp65 antibody. **Lane 2**: HIV-I infected cells precipitated with anti-HIV patient serum. **Lanes 3 and 4**: cell lines expressing pp65 precipitated with anti-pp65 antibody. **Methods:** Two adenoviral expression vectors, pACCMVpLpA/pp65 and pACCMVpLpA/pp150, were developed. The genomic HCMV pp65 (1750 bp) and pp150 (3150 bp) sequences were amplified by polymerase chain reaction (PCR) from primers that introduced *Bam*HI and *Xba* I, and *Xba* I and *Hind* III restriction sites, respectively, at the ends of the amplified DNA. Both PCR amplification products were cloned downstream of the CMV major immediate-early promoter (MIEP) in the shuttle plasmid vector pACCMVpLpA. This plasmid contains an adenovirus origin of replication and encapsidation signal upstream of the transgene insertion, and a downstream polyA tail followed by about 3000 bp of adenovirus 5 DNA, to provide a substrate for recombination into the backbone of the adenovirus strain, dl309, in 293 cells. The transgene replaces the adenovirus E1a and E1b gene regions. Recombinant adenovirus was obtained by transfection of linearized plasmid and DNA from adenovirus strain dl309 introduced into 293 cells that constitutively provide the E1a and E1b gene functions for complementation of recombinant virus *in trans*. Recombinant virus plaques were identified by restriction enzyme analysis of candidate strains and designated Adpp65 and Adpp150. After 3 successive plaque purifications and amplification of a representative plaque, high titer (10^{10} pfu/mL) recombinant virus stocks were purified on CsCl density gradients.

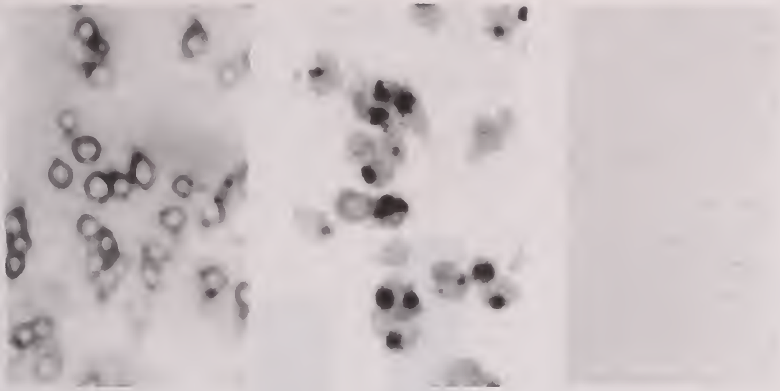

Fig. 2. Expression of pp65 by human DC transduced with Adpp65 at multiplicity of infection of 100. **(Left)** Late cytoplasmic expression of pp65 by transduced DC. **(Middle)** Early nuclear expression of pp65 by transduced DC. **(Right)** Negative control cells (non-transduced cells). **Methods:** Mature mouse DC were obtained from spleen using techniques established in the laboratory (50).

Adpp65 recombinant was used to infect primary dendritic cells *in vitro*, and the results showed that Adpp65 produced efficient (>35%) transduction and high level expression of pp65 in cultures of primary DC. Noteworthy is the fact that the pp65 protein was expressed both in the nucleus and at the cell surface. However, the cell surface expression appeared at a later time point after infection with the recombinant. In several experiments the transduction frequency was comparable (20–35%) to that in previous experiments using adenovirus-mediated expression of lacZ (51).

We next wanted to test the efficacy of pp65-transduced DC in stimulating pp65 CTL responses *in vivo* (Fig. 3). Balb/c (H-2^d)-derived DC transduced with recombinant adenovirus expressing pp65 were used for *in vivo* immunization of mice to induce anti-pp65 CTL responses. The results showed that strong and specific CTL responses were generated in H-2^d mice against the CMVpp65 protein after vaccination with 1×10^6 live H-2^d DC expressing pp65 (middle closed column). Furthermore, this antiviral response was higher than that of the response primed against allo-MHC (right closed column). The pp65-specific CTL response is comparable to that of HIV-nef-specific CTL responses reported by using a similar experimental system (52). Conversely, control P815 (H-2^d) cells which do not express pp65 were not lysed (left closed column). Mice immunized with 1×10^6 P65 (H-2^d) cells which express pp65, in combination with similar numbers of Balb/c DC (H-2^d) (not expressing pp65) did not lyse P65 (H-2^d) target cells when restimulated with H-2 mismatched B6 splenocytes, but an appropriate allo-MLR (mixed leukocyte response) response was generated (open columns).

Conclusions

One feature of cytomegalovirus (CMV) infection is a transient but severe immunodeficiency that characterizes the initial stages of the infection process (53). Recently, a role of DC in the CMV-associated immune deficiency has become appreciated. The effects of CMV infection with respect to interference with the immune functions of DC is key to the rationale of approaching vaccination against CMV by enhancing DC-mediated immune responses against CMV. CMV has been shown to infect DC (54–58), to impair maturation (57, 58) and antigen presentation by DC (58), and to impair allostimulatory capacity of DC (58). These findings make DC a rational target for gene transfer in the context of CMV immunization. We hypothesize that transplant recipients would obtain improved protection against reactivation of *de novo* CMV infection if effective CTL responses could be generated prior to the scheduled transplant. Likewise, HIV-1 infected individuals might benefit from induction of CMV-directed CLT responses earlier in the disease,

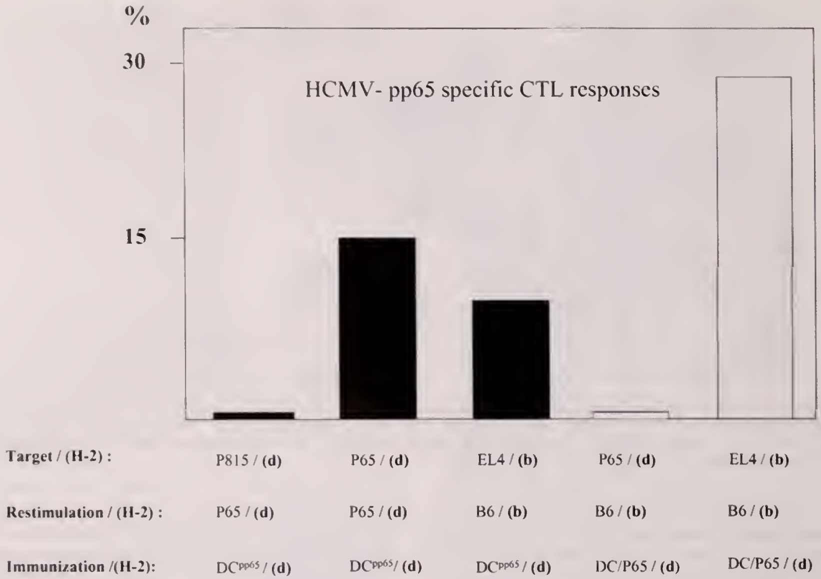

Fig. 3. HCMV-pp65-specific CTL responses (%) against target P65 cells (H-2^d) relative to allo-MHC responses (H-2^b). **Closed columns**: For induction of pp65-specific CTL, Balb/c DC (H-2^d) expressing the pp65 recombinant were used for immunization of Balb/c mice (primary stimulation) by injection of approximately 1×10^6 transduced DC per mouse. After 12 days the splenocytes from the primed mice were restimulated (secondary stimulation) *in vitro* with P65 [a P815 (H-2^d) derivative expressing HCMV pp65], or B6 (H-2^b) splenocytes: ^{51}Cr-labeled target cells for CTL assays (% release) were P65 [a P815 (H-2^d) derivative expressing HCMV pp65], P815 (H-2^d), or EL4 (H-2^b). To establish stable cell lines expressing high levels of pp65, a pp65 expression plasmid was transfected into the P815 cell line, along with pSV2neo for neomycin selection. This cell line, P65 (H2^d), was the target cell for the CTL assays. **Open columns:** Same experimental setup, except that approximately 1×10^6 DC (H-2^d) with no pp65 expression in combination with a similar number of P65 cells were used as stimulators.

when CD4$^+$ T cells are not depleted. In fact, studies in Rhesus Macaques infected with pathogenic simian immunodeficiency virus (SIV) have shown CMV-specific CTL activity earlier in the disease (59).

Adenoviral vectors are currently among the most efficient vehicles of gene transfer for both *in vivo* and *in vitro* gene delivery, though their potential use in clinical practice in the future may be limited. One experimental concern with the use of the adenovirus delivery system is the possibility that competing immune responses (e.g., neutralizing antibodies) may be raised against vector-derived antigens rather than the gene of interest (60–62). Our preliminary results using primary DC suggest that competitive anti-adenovirus immune responses are not a limitation for the short-term use of an adenoviral delivery system. This may be because of either the limited number (1–2) of challenges, the limited dose of virus given with washed DC, or a protective effect of DC. In fact, recent evidence suggests that transduced DC can protect against induction of neutralizing antibody responses (Th2 responses) (63, 64). In these reports, administration of adenovirus alone resulted in high titers of antiviral antibodies that inhibited adenoviral infection of 293 cells, whereas the sera of mice injected with infected DC showed only low levels of blocking activity (64). At present there is no explanation for this "protective" effect of DC against antiviral antibodies. It can be speculated that preferential intracellular expression of antigen by DC would favor generation of cellular class I restricted responses. Hamel at al. have recently showed that adenovirus-transduced DC are able to generate efficient CTL responses against adenovirus and CMV simultaneously (65). The development of adenoviral vectors that are deleted in all viral protein coding sequences (gutted vector) offers the prospect of using less immunogenic vectors.

A different scenario with the use of an adenovirus gene delivery system is the possibility that synthesis of adenovirus gene products will interfere with the expression of pp65 or the subcellular compartmentalization of the pp65 antigen. The gp19 protein encoded within the E3 adenovirus gene region causes intracellular entrapment of MHC class I products, but may also cause nonspecific entrapment of non-HLA-related surface proteins encoded by the vector (66). The strain of adenovirus (dl309) used for recombinant construction in our studies expresses gp19, and entrapment of MHC molecules could render the transduced DC less efficient as antigen/peptide presenting cells. At present, our studies suggest that the pp65 antigen is efficiently expressed in the nucleus, cytoplasm, and cell membrane.

DNA vaccination with plasmids expressing HCMV proteins is a possible future avenue of vaccination. However, recent literature suggests that the mechanisms underlying DNA vaccination, while poorly understood, are in fact dependent on professional antigen-presenting cells such as DC, which are key leukocytes for immune stimulation with DNA (67–72).

Currently several clinical trials of tumor vaccination with *ex vivo*-generated DC are ongoing, but the outcome results are pending (73). Similar studies of HCMV vaccination with *ex vivo*-generated DC may prove to be more efficacious in a system where the antigen is much better defined.

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The Multidisciplinary Approach to Hemodialysis Vascular Access at The Mount Sinai Hospital

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Abstract

A majority of the quarter of a million end-stage renal disease patients nationwide are treated with hemodialysis. Important and frequent causes of morbidity and mortality, when they undergo this procedure, include vascular access infection and thrombosis associated with the use of catheters and, to a lesser extent, grafts. Therefore, an arteriovenous (AV) fistula is the preferred hemodialysis access. A multidisciplinary approach, including nephrologists, vascular surgeons, interventional radiologists, nurses, nephrology fellows, and nephrology physician assistants, meeting together weekly, should improve hemodialysis outcomes by promoting the use of AV fistulas. The specific roles of the interventional radiologist, vascular surgeon, nephrologist and other members of the multidisciplinary team are reviewed. Important additional components of this program are Doppler ultrasound for preoperative hemodialysis access vein mapping and screening techniques for early detection of arteriovenous graft stenosis. The use of arteriovenous fistulas in the Mount Sinai outpatient hemodialysis program has increased from 15% to 43% ($p<0.001$) and substantially limited catheter use since 1998, when the multidisciplinary program began.

Key Words: Dialysis, AV fistula, graft, catheter, vein mapping, Doppler ultrasound, static venous pressure, thrombolysis, distal revascularization interval ligation.

Introduction

THE END-STAGE RENAL DISEASE (ESRD) program in the United States has grown 100-fold, to approximately one quarter of a million patients, since Congress approved Medicare coverage of renal replacement therapy in 1972 (1). Although this represents a genuine medical success story, there are some negative aspects. Currently, vascular access procedures and their complications represent major causes of morbidity and mortality for chronic hemodialysis patients, with an estimated annual health care cost approaching $1 billion (2).

The arteriovenous fistula (AVF) is the preferred hemodialysis access with the lowest risk of infection and thrombosis (3). Unfortunately, recent data show only 28% functional AVF and 24% catheter prevalence in U.S. hemodialysis patients (4), in contrast to an 80% AVF prevalence in Western Europe (5). Although several risk factors associated with poor AVF outcomes, such as advanced age, diabetes, African-American ethnicity, obesity, and female gender are well represented in the U.S. dialysis population, this is unlikely to be solely responsible, given the 0 – 87% AVF prevalence range for individual centers nationwide (5).

A multidisciplinary approach to hemodialysis vascular access should increase the percentage of AVF created, preserve each access site for as long as possible, and limit tunneled and cuffed catheter (TCC) use. The following sections will review the roles of the interventional radiologist, vascular surgeon and nephrologist, and of the multidisciplinary team, in vascular access planning and management.

Interventional Radiology

The role of the interventional radiologist is to provide and maintain adequate vascular access as long as possible, to avoid delays and/or

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interruptions in hemodialysis therapy. Factors that complicate the management of dialysis access include: the limited number of potential access sites in each patient, the limited lifespan of each site, and the natural occurrence of stenoses/thromboses, particularly in the case of arteriovenous grafts (AVG). The interventional radiologist is essential for the placement, management and removal of TCC and the management of poorly functioning AVF and AVG.

Tunneled and Cuffed Catheters

TCC provide temporary vascular access, with advantages including ease of insertion and immediate use. Indications for TCC are maturing AVG or AVF, failure of either current access site or peritoneal dialysis, and acute renal failure requiring hemodialysis for more than three weeks (3). These catheters should be preferentially placed in the right internal jugular vein (Fig. 1), since this site confers the lowest complication rate (3). Other placement options include the right external jugular and left internal and external jugular veins. The brachiocephalic vein and collateral veins offer alternative access sites for patients with occluded internal and external jugular veins. Subclavian vein catheterization should be avoided unless there are limited alternatives, because central venous stenoses and occlusions frequently follow catheter placement at this location (3). Femoral, translumbar, and transhepatic vein TCC may also be used only in exceptional circumstances, since these sites are associated with high complication rates. Catheter insertion using real-time ultrasound guides placement and also reduces complications, since venous anatomy varies (3, 6).

Catheter malfunction secondary to pericatheter fibrin sheath and thrombus formation is common, often limiting duration of catheter utility. Late catheter malfunction results from thrombosis or fibrin sheath formation. Treatment options include percutaneous fibrin sheath stripping, performed in the interventional radiology suite or thrombolytic TCC instillation (7). The latter is noninvasive and safe, and can be performed in the outpatient dialysis unit, using 1 mg/mL alteplase or 0.4 U reteplase to fill luminal volume. One prospective study of alteplase for catheter malfunction revealed limited efficacy after 3 instillations (8). If thrombolytic therapy fails to restore catheter function, catheter exchange should be considered, after imaging to identify the cause of malfunction.

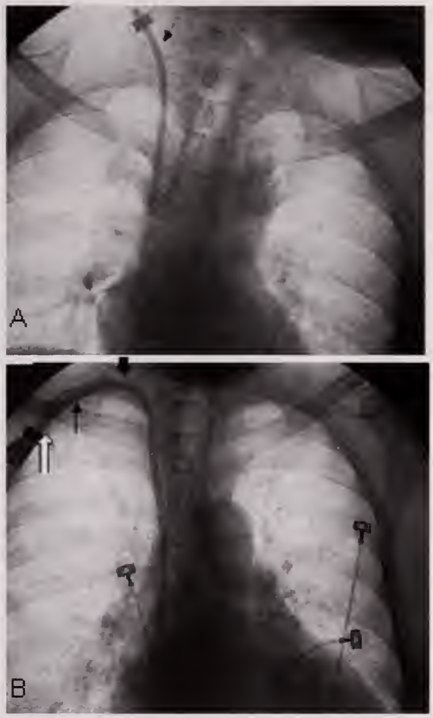

Fig. 1. Double lumen hemodialysis catheter types include the right internal jugular vein uncuffed catheter shown in panel **(A)** with venotomy and catheter exit site at the same position (black arrow) and catheter tip in the right atrium. The right internal jugular vein tunneled cuffed catheter (TCC) is shown in panel **(B)**, with the approximate venotomy site (wide black arrow), approximate cuff location (thin black arrow), and exit site (white arrow). The subcutaneous tunnel is located between the large arrows and the TCC tip is in the right atrium.

Arteriovenous Fistulae

Although the AVF is the preferred vascular access (3), the disadvantages of AVF include: 3–4 month maturation, possible need for TCC to initiate dialysis, failure of outflow vein to enlarge sufficiently to allow for repeated cannulation by 16- or 15-gauge needles, and unappealing cosmetic appearance of enlarged veins. The radiocephalic AVF, followed by brachiocephalic AVF, are preferred as optimal sites (3).

A major problem of AVF is failure to mature in approximately a third to up to half of cases (9). Failure of maturation can be attributed to:

inadequate arterial inflow, outflow vein stenosis, poor surgical anastomosis, and development of collateral veins that delay maturation by siphoning flow (10). The examination of a maturing AVF should focus on the caliber of the fistula and the quality of the thrill. Collateral veins may be obvious on clinical evaluation or detected only by temporary finger occlusion of the AVF (10). Stenoses (inflow and outflow) should be treated with percutaneous transluminal angioplasty (PTA). If PTA fails, surgical revision or new AVF insertion should be considered. Most stenoses occur in the outflow vein at the point of vein mobilization during the initial AVF construction, known as swing-point stenoses (11). The interventional radiology group at Mount Sinai recently demonstrated PTA to be safe, and efficacious in establishing adequate blood flow at swing-point stenoses in non-maturing or poorly functioning AVF (11).

When a mature AVF can no longer sustain adequate blood flow, intervention is recommended to prolong the fistula life (3). Etiologies for poorly functioning AVF are outflow vein stenoses or progressive atherosclerotic disease. The quality of the thrill over the entire portion of the AVF should be the crux of the examination. Failing AVF may present with decreased thrill or pulse alone, elevated venous dialysis pressures, abnormal urea recirculation, decreasing dialysis dose delivery, decreasing flow rates, difficulty in cannulating, or prolonged post-dialysis bleeding (10). However, these findings occur late and are not as sensitive as in AVG screening.

The treatment of thrombosed AVF is more challenging than that of poorly functioning AVF. There is controversy in the interventional radiology community regarding the long-term patency of salvaged thrombosed AVF. A recent report demonstrated excellent results in AVF percutaneous thrombectomy using thromboaspiration, mechanical devices, or thrombolytic drugs in combination with PTA (12).

Arteriovenous Grafts

After AVF possibilities are exhausted, AVG is the next best option for hemodialysis vascular access (3). The most common cause of AVG failure is the development of intimal hyperplasia at the site of venous anastomosis, which progressively leads to thrombus formation, graft occlusion, and arterial clot extension (3). Other AVG thrombosis etiologies include arterial and mid-graft stenosis, severely impaired cardiac output, hypotension, hypercoagulability, or rarely, excessive external compression. The salvage of thrombosed AVG can be achieved using thrombectomy (mechanical/surgical/balloon), pulse-spray pharmaco-mechanical thrombolysis, and infusion or instillation of thrombolytic agents to restore flow and re-establish patency. Unlike AVF, occluded AVG are more amenable to thrombolysis (which is typically done in combination with PTA) (Fig. 2). Combinations of PTA and 1 unit reteplase plus 4,000 IU heparin or 2 mg tissue plasminogen activator (tPA) plus 3,000–5,000 IU heparin have been shown to be efficacious and safe for the treatment of thrombosed AVG (13, 14). This modified thrombolysis and PTA technique allows for a rapid occlusion resolution in the angiography suite. The addition of thrombolytic agents in the management of occluded AVG is particularly important for reducing the risk of pulmonary embolism.

Central Venous Disease

The clinical signs of central venous disease include the presence of upper extremity edema, facial edema, and collateral veins over the ipsilateral upper arm, neck, and chest wall. The vascular access usually remains patent. Stenoses should be managed primarily with PTA (3). Occlusions and lesions refractory to PTA should be treated with stents. The Mount Sinai interventional radiology program follows occluded central veins after PTA and/or stent insertion every 6–8 weeks to maintain patency, monitor for recurrence of symptoms, and assist in the preservation of ipsilateral access function. The frequent recurrence of central venous lesions supports this approach.

Vascular Surgery

Procedures for hemodialysis access are the most common vascular surgical operations in the United States, representative of the growing number of ESRD patients (15). A recent report found that AVG are used 1.7 times more often than AVF (16), in part as a result of quicker AVG maturation and the high early AVF-failure rate. Upper limb arteries and veins most suitable for vascular access should be selected before the diagnosis of ESRD is established.

Vascular Screening Using Doppler Ultrasound

Three vascular access screening techniques are history and physical examination, Doppler

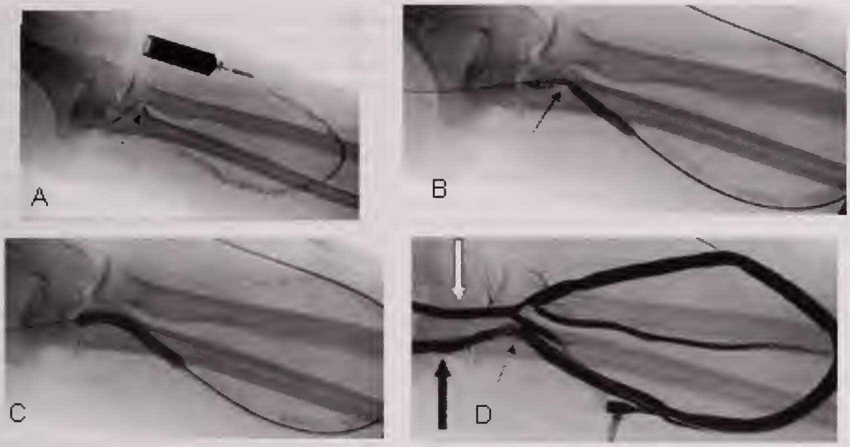

Fig. 2. A thrombosed forearm arteriovenous graft (AVG) undergoes percutaneous thrombolysis and angioplasty (PTA). Panel (**A**) demonstrates clot as filling defects within graft. Venous anastomosis is shown by arrow. Panel (**B**) following thrombolysis, PTA is performed at the venous anastomosis. The waist on the balloon identifies the venous anastomotic stenosis (arrow) responsible for AVG thrombosis. Panel (**C**) shows the balloon fully inflated to 18 atm pressure, to facilitate the obliteration of the stenosis. Panel (**D**), the post-procedure angiogram reveals patent inflow/brachial artery (white arrow), AVG, venous anastomosis (thin black arrow) and outflow/basilic vein (wide black arrow).

ultrasound, and venography. Screening should be performed not only before the diagnosis of ESRD is established, but also at any time a patient's access is being revised or replaced. A history of previously failed vascular accesses will limit available sites for access; the cause of a previous failure may influence future access planning. Hemodialysis AVG or AVF should never be placed on the same arm as an existing transvenous pacemaker or an existing subclavian catheter unless there are no other options. Although Doppler studies are reliable for peripheral venous and arterial assessment without contrast, venography is more accurate for evaluating central veins. Cost, invasive nature, and radiocontrast nephrotoxicity in chronic kidney disease (CKD) patients limit venography indications to those access candidates with upper extremity edema, collateral vein development, current or previous subclavian catheter placement, pacemaker placement, previous arm, neck, or chest trauma, and multiple previous accesses (3). For patients who do not have venography indications, preoperative Doppler screening is performed. Vein mapping is superior to clinical examination for identifying veins suitable for AVF construction.

Although Doppler ultrasound is an invaluable tool for vascular access assessment of the hemodialysis patient, few studies have examined the utility of vascular mapping before hemodialysis access insertion. Silva and colleagues (17) suggest that the inability to predict adequacy of venous outflow based solely on clinical examination, and the consequent use of suboptimal veins and arteries has resulted in high AVF failure rates and increased usage of AVG. This group developed a noninvasive preoperative protocol to increase AVF by identifying veins that were not clinically evident. This group was the first to prospectively demonstrate an increase in AVF construction from 14% to 63% using Doppler ultrasound vein mapping. The preoperative criteria for creating a successful upper extremity AVF were diameters of 2 mm or larger for arteries and 2.5 mm for veins.

Robbin's group (18) compared the original operative plan based on clinical assessment alone versus that using Silva's criteria. Fifty-two of 70 patients who underwent ultrasonographic mapping had vascular accesses placed. Preoperative ultrasonographic mapping resulted in a change in the planned surgical procedure for 16 (31%) of the 52 patients. An AVF rather than the planned AVG was placed in 8 (15%) patients. Overall, 30 (58%) of the 52 patients had an AVF placed compared to 126 (32%) of

395 previous patients who had not undergone preoperative mapping. An additional 17-month prospective series of preoperative Doppler at the same center demonstrated an increase in AVF creation from 34% to 64% when compared to historical controls without consistent vein mapping (19).

Patients who meet the following vein mapping criteria (20, 21), developed by Dr. Teodorescu, are selected for AVF insertion:

1. Cephalic or basilic veins measuring at least 2 mm in diameter in continuity with the deep system.
2. An appropriate artery measuring at least 2 mm in diameter with peak systolic velocity of 50 cm/sec or greater.
3. Patent ipsilateral subclavian vein.

The criteria for preoperative noninvasive screening were developed in 1998 by extrapolating lower extremity vein bypass graft data (22). Since success was reported with the use of veins as small as 2 mm, this caliber was adopted as the criterion for the ability to create an AVF. Vein diameter varies with volume status, and therefore a single small measurement was not enough to eliminate the possibility of creating an AVF. Venous duplex ultrasound was performed without the use of a tourniquet, unless veins smaller than 2.5 mm were identified. The ability of a small vein to dilate to a diameter 110% greater or more with tourniquet application was taken as an indication that the vein was suitable for use as a fistula.

An AVF should be created when the glomerular filtration rate (GFR) falls below 30 mL/min (23). The poor patency rate of AVG due to thrombosis may require its creation several weeks before dialysis becomes necessary.

A majority of patients undergoing access Doppler screening meet the above criteria and are thus able to undergo AVF creation. The most common reason for AVG placement is upper extremity veins measuring less than 2 mm in diameter or veins that are calcified. Retrospective series of Mount Sinai's preoperative ultrasound Doppler screening program demonstrate particular benefit in diabetics (20) and obese patients (21), in whom the use of AVF is otherwise infrequent.

"Steal" Syndrome

An uncommon, 1.8–4.3% (24), but potentially devastating upper arm AVG and AVF complication is distal upper limb ischemia, which occurs when the access diverts brachial artery blood flow leading to ischemia of tissues supplied by the arterial vessels distal to the access site. Other risk factors include diabetes and peripheral vascular disease (24). This complication is less common with forearm AV access. Prevention of "steal" syndrome is an important aspect of preoperative vascular screening. Such screening should include measuring the blood pressure in both upper extremities and performing the Allen test bilaterally, as well as taking the appropriate Doppler ultrasound measurement of arterial caliber and peak systolic velocities.

Although the diagnosis of steal syndrome is frequently obvious, angiography before and after occlusion of the dialysis access definitively establishes etiology and assists the surgeon in planning intervention.

If ischemia occurs, the vascular surgeon must make a clinical decision regarding the optimal technique to restore or improve flow to the ischemic segment. Ligation of the access is the optimal procedure to treat ischemia, but leaves the patient no alternative other than catheter access. Partial limitation of access flow, commonly referred to as "banding," initially preserves the access and improves distal perfusion. However, this procedure severely limits the access patency (25). An important alternative is distal revascularization with interval ligation (DRIL), developed at Mount Sinai by Dr. Harry Schanzer and colleagues (26). This innovative form of bypass surgery has the unique advantage of both preserving access flow and restoring flow to the ischemic segment (25–27). Increasingly, DRIL is being recognized as the surgical intervention of choice (27).

Pseudoaneurysms

Whereas aneurysms are associated with AVF, pseudoaneurysms are an AVG complication. Prevention of progression is achieved by avoidance of needle insertion into the area of pseudoaneurysm or aneurysm. Indications for pseudoaneurysm resection and insertion of an interposition graft include rapid expansion in size, size exceeding twice the AVG diameter, possible or impending rupture, compromised overlying skin, and infection (3).

Nephrology

The nephrologist is uniquely responsible for the management of the patient with renal failure, both before and after the initiation of dialysis therapy. However, the development of an access plan for the patient well in advance of dialysis is best accomplished in a multidisciplinary fashion. Patients with CKD should be considered for hemodialysis access, peritoneal dialysis, and transplantation, when their glomerular filtration rate (GFR) is less than 30 mL/min (23). According to the National Kidney Foundation's recent Clinical Practice Guidelines for CKD, patients should be prepared for dialysis at this level of GFR, using the updated Modification of Diet in Renal Diseases (MDRD) equation (28). This simplified equation uses age, race, gender, and serum creatinine to determine GFR (29). Early referral to a nephrologist is associated with decreased TCC prevalence at the time of dialysis initiation (30). Ten guidelines for dialysis access are listed in the Table.

Catheters

Catheters are consistently the dominant culprit for bacteremia (31). *Staphylococcus aureus* is the most common bacteremia in this setting, causing endocarditis in 12% of patients in one prospective series (31). Infection is the second leading cause of death for dialysis patients (1). Therefore, limiting the use of catheters is an important infection control measure.

TABLE

Ten Hemodialysis Access Guidelines

1. Discourage use of TCC as permanent access in individual patients.
2. At programmatic level, aim to limit TCC to less than 10% of hemodialysis population.
3. Limit uncuffed catheter use to 3-week duration if internal jugular, 1-week duration if femoral.
4. Avoid subclavian TCC and uncuffed catheters, to reduce the risk of subclavian vein stenosis/occlusion, unless options are limited.
5. Avoid the peripherally inserted central catheter (PICC), which promotes vein thrombosis and/or sclerosis in chronic kidney disease and hemodialysis patients.
6. Refer established CKD patients with GFR less than 30 mL/min for vascular access if hemodialysis is the choice for renal replacement therapy.
7. Consider peritoneal dialysis and renal transplantation for all CKD patients with GFR less than 30 mL/min, and for all hemodialysis patients, particularly during access failure.
8. Preserve selected access arm both preoperatively and after intervention, by avoiding venipuncture, BP monitoring, and finger-stick glucose testing.
9. Reassess patients for AVF at every instance of new access placement.
10. Screen all hemodialysis candidates using Doppler ultrasound vein mapping to promote AVF.

Catheter malfunction secondary to thrombosis or more complex fibrin sheath formation is common and an important cause of patient frustration and inadequate dialysis dose delivery. Prevention with instillation of heparin in the catheter ports after dialysis is the most commonly employed measure. One randomized trial showed that 2 mg tPA was superior to 2,000 IU heparin for TCC priming between hemodialysis sessions and that it can be used as an expensive but more effective alternative to conventional heparin in selected patients (32). Oral warfarin 1 mg daily or mini-dose was not efficacious in a prospective, randomized, placebo-controlled trial for prevention of TCC malfunction in hemodialysis patients, in contrast to trials in oncology patients with catheters (33). There are no randomized trials to date to support the use of warfarin therapy to prevent dialysis access malfunction in the absence of a documented hypercoagulable state.

The lower blood flow rates and increased incidence of thrombosis which occur with TCC compared to AVF is often associated with inadequate dialysis dose as measured by urea kinetics. Reducing the use of TCC is one of the simplest ways to enhance dialysis dose delivery in an ESRD population (34). Moreover, a random nationwide study of more than 5,000 hemodialysis patients demonstrated that subjects treated with TCC had an increased adjusted mortality risk (RR 1.7, $p<0.001$ for non-diabetics, and RR 1.54, $p<0.002$ for diabetics) compared to those treated with AVF (35).

Subcutaneous Port

The recently FDA-approved LifeSite® (Vasca, Inc., Tewksbury, MA) is a novel form of hemodialysis access, composed of two titanium subcutaneous ports and two separate catheters. The system requires special training, experience, and the use of 70% isopropyl alcohol antimicrobial solution instilled in each port after each treatment. Although advantages may include increased blood flow (36), decreased infection rates (36), and better cosmetics than TCC, the exact role of this new access technology is not established. The treatment of port-related bacteremia is complex, requiring daily isopropyl alcohol instillations as well as antibiotic therapy. If treatment fails, device removal is not a trivial procedure.

AVG Screening

A recent series demonstrated that 77% of AVG required surgical or interventional radiology intervention to maintain patency at one year. Additionally, 45% of AVG permanently failed, requiring replacement in this interval (37). Late referral of patients to interventional radiology when AVG thrombosis was suspected may have resulted in these outcomes. The aim of AVG surveillance is to detect stenosis early, before progression to thrombosis occurs. AVG screening techniques — the responsibility of the nephrologist in the dialysis unit — include history, physical examination, inspection for adequacy of dialysis, dynamic venous pressure evaluation, static pressure (SP) monitoring and access flow measurements. Important physical findings include edema, prolonged bleeding after needle withdrawal (venous hypertension associated with stenosis), and altered characteristics of the AVG pulse or thrill (3). A change in pitch of the thrill or conversion of the thrill to a pulse represents turbulent flow in a stenotic segment. The examination is most useful when performed and evaluated by the same health care worker.

The maintenance of a well-functioning vascular access for hemodialysis is critical. Any stenosis at either the site of the venous or arterial anastomosis, or within the access itself, would impair systemic blood flow rate and/or increase the extent of recirculation of blood to the hemodialysis machine and thereby reduce the efficiency and effectiveness of the dialysis procedure. Such stenosis could lead to ultimate thrombosis of the access. Accordingly, the detection of a significant and progressive stenosis would be important. The least sensitive technique is dynamic venous pressure monitoring that measures venous pressure at blood flow of 200 mL/min during dialysis. A more sensitive diagnostic tool to accomplish this includes periodic monitoring (once or twice a month) and uses intra-access static pressures (SP), a readily available simple procedure. The intra-access pressures are measured using dialysis cannulation needles before the procedure is initiated. At the same time, the systemic mean arterial pressure (MAP) is measured in the contralateral extremity. Significant change in the ratios of the static intra-access pressure to that of the MAP, particularly of the venous pressure ratio, as the access matures and is used has been found by some investigators to be helpful in predicting the extent of a stenosis and the probability of thrombosis (38). Other useful monitoring methods are that of Doppler ultrasonography, the measurement of the extent of recirculation (3, 38, 39), and the measurement of access flow rate by ultrasound velocity dilution technique (40). This latter procedure, not now reimbursed by Medicare, requires special training, and brief interruption of the dialysis. At the present time, few centers use this technique. Angiography of the intravascular access is the most invasive of the various tools and may be required when other less invasive methods yield uncertain conclusions as to the locus, extent and significance of a suspected stenosis.

Medical Prophylaxis for AV Access

Dipyridamole (41) and fish oil (42) were each demonstrated to benefit AVG patency in small randomized trials. Although aspirin is appropriately prescribed to dialysis patients for prevention of coronary events, aspirin alone showed no benefit in AVG thrombosis prophylaxis in one study (38). Results using the combination antiplatelet therapy of clopidogrel 75 mg and aspirin 325 mg were disappointing compared to placebo, with significantly more bleeding events and a small but insignificant AVG patency benefit in the treated group (43). A majority of patients with isolated, recurrent AVG thrombosis have no demonstrable hypercoagulable state (3). Although warfarin is occasionally used to treat recurrent AVG thrombosis, this therapy did not improve patency compared to placebo, and was associated with significant clinical hemorrhage in a recent prospective, randomized study (44). Warfarin should be reserved only for those patients with a documented hypercoagulable state such as antiphospholipid antibody syndrome, for which benefit is clearly supported (45). Those effected may have other manifestations of hypercoagulability, such as previous miscarriage, pulmonary embolism or deep venous thrombosis. Given the complex pathophysiology of AVG thrombosis, including endothelial hyperplasia at the venous anastomosis, the disappointing results with anticoagulants are not surprising. Even when there was a clear anti-coagulation indication, warfarin therapy was associated with a 10% significant hemorrhage rate in the hypercoagulable hemodialysis patients in the study be LeSar et al. (45). Major weaknesses of prior studies include patient selection from single centers and varying frequencies and methods of AVG stenosis screening. The NIH Dialysis Access Consortium is conducting a multicenter trial to provide more definitive results regarding the safety and efficacy of aggrenox (aspirin 25 mg/dipyridamole 200 mg) in prophylaxis of AVG thrombosis. Although this promising study design overcomes many flaws of previous trials, it prolongs the current and mostly disappointing era of antiplatelet therapy for fostering AVG patency. The next important phase in this area is likely to target neointimal hyperplasia.

Early referral to a nephrologist is also associated with a higher prevalence of AVF at the time hemodialysis therapy is initiated (46). There are very few trials of medical therapy to enhance early AVF patency. The NIH Dialysis Access Consortium is also conducting a randomized, placebo-controlled trial of clopidogrel in AVF maturation. The AVF stenosis screening methods are similar to those for AVG, but are generally less sensitive.

The Multidisciplinary Team

The Mount Sinai multidisciplinary vascular access team, organized in 1998, comprises nephrologists, vascular surgeons, interventional radiologists, nephrology fellows, a dialysis unit physician assistant, and dialysis unit nurse managers, who meet weekly to review hemodialysis candidates with GFR less than 30 mL/min., patients new to hemodialysis, complex cases, overall access prevalence, and all catheter patients. Major aims of the team are to align goals, foster communication, and share expertise to improve patient outcomes. Such a group here and at other institutions (47, 48) have selected the use of an access coordinator as the focal point in the organization of the team. The nephrologists provide feedback to an interventional radiologist regarding blood flow and dialysis delivery after angioplasty of an AVG venous stenosis. The nephrologists are also able to identify access steal in a particular patient on the basis of the vascular surgeon's targeted clinical examination. The recurrent AVG thrombosis case is reviewed by the team, to determine the optimal intervention (repeat thrombectomy, surgical revision, or new access placement). The team approach also provides opportunities to review AVF options, especially when an AVG requires revision. The multidisciplinary approach and the Doppler screening protocol have increased AVF prevalence from 15% to 43% ($p<0.001$) and reduced TCC prevalence from 44% to 25% ($p<0.001$) as of February 2003. In fact, many individual cases could be used to illustrate the effectiveness of the team approach. Access outcomes are followed prospectively as part of the quality assurance process. While our current practice falls short of the nationwide goal of resorting to TCC in less than 10% of patients, substantial progress has been made in this direction. Recent nationwide data indicate that 28% of the patients are receiving AVF, while 24% are receiving either TCC or uncuffed catheters (4).

Conclusion

The multidisciplinary approach to hemodialysis access, including weekly conferences, succeeds in aligning aims, facilitating communication and collecting access outcome data prospectively. Most important, when combined with Doppler ultrasound for preoperative vein mapping, it has significantly increased the use of AVF and limited chronic catheter use.

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Grand Rounds

Current Medical Treatment of Pulmonary Arterial Hypertension

Roxana Sulica, M.D.[1], and Michael Poon, M.D.[2]

Abstract

Primary pulmonary hypertension is a rare disease of the pulmonary vasculature manifested by dyspnea on exertion, syncope, and signs and symptoms of right heart failure. In the absence of adequate treatment, primary pulmonary hypertension has a grave prognosis, with a median survival of 2.8 years. Pulmonary arterial hypertension develops in association with known risk factors and predisposing clinical conditions, and shares many clinical, pathological and therapeutic characteristics with primary pulmonary hypertension. Therapeutic choices in pulmonary arterial hypertension depend on the etiology of the disease, severity of functional impairment and hemodynamic response following acute vasodilator administration during right heart catheterization. Agents currently approved for the specific treatment of pulmonary arterial hypertension are continuous intravenous epoprostenol, subcutaneous treprostinil and oral bosentan. A small group of patients who demonstrate true acute vasoreactivity at right heart catheterization may be chronically treated with oral calcium channel blockers. In addition, most patients with pulmonary hypertension receive conventional treatment, represented by anticoagulants, diuretics, inotropic medication or oxygen supplementation. Treatment of pulmonary arterial hypertension has significantly altered the natural course of the disease, with pronounced symptomatic, functional and survival benefit. Current clinical research focuses on the discovery of new targets of therapy and the use of a combination treatment approach, which will offer hope and valuable insight into the pathogenetic basis of this devastating illness.

Key Words: Primary pulmonary hypertension, pulmonary arterial hypertension, treatment, prostacyclin, endothelin receptor antagonist, epoprostenol, treprostinil, bosentan.

Introduction

PULMONARY HYPERTENSION (PH) is a heterogeneous group of disorders characterized by increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Without intervention, PH has a progressive downhill course, leading to right ventricular failure and death. Diagnostic classification of PH includes five major categories of diseases, based on similar biologic, etiologic, clinical and therapeutic characteristics (1) (Table 1). Primary pulmonary

TABLE 1
Diagnostic Classification of Pulmonary Hypertension

Pulmonary Arterial Hypertension

- Primary Pulmonary Hypertension (PPH):
  - sporadic
  - familial
- Related to:
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs/toxins: anorexigens and others
  - Persistent pulmonary hypertension of the newborn

Pulmonary Venous Hypertension

Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia

Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease

Pulmonary Hypertension due to Disorders Affecting the Pulmonary Vasculature

Adapted from the Executive Summary — World Symposium on PPH 1998 (1).

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hypertension (PPH) has no apparent cause, while other forms of PH are associated with known risk factors or develop as a consequence of other co-existing disease states. All forms of diseases included under the pulmonary arterial hypertension (PAH) category have similarities with PPH in terms of pathologic characteristics, clinical presentation, diagnostic modalities and therapeutic options. If PPH remains untreated, its prognosis is extremely poor, with an estimated median survival, based on the National Institutes of Health (NIH) Registry of 194 patients, of 2.8 years and 1-, 3-, and 5-year survival rates of 68%, 48% and 34%, respectively (2). The most important determinant of survival is the level of right ventricular function, and the most common cause of death is right ventricular failure (2–4).

The pathologic hallmark of PAH consists of the triad of vasoconstriction, vascular wall remodeling and thrombosis (5, 6). Pulmonary vascular endothelium dysfunction plays a crucial role in the pathogenesis of pulmonary hypertension. Specifically, there is an imbalance between endothelial mediators with opposing actions on pulmonary vasculature (7–11). There is an overexpression and/or activation of vasoconstricting, mitogenic and prothrombotic factors (endothelin-1, thromboxane and serotonin) and a decrease in prostacyclin, nitric oxide and heparin-like substances, which promote vasodilatation and have antiproliferative and antithrombotic properties. Current treatment of PAH focuses on either replacing deficient vasodilating factors and growth factor inhibitors, or inhibiting mediators that induce vasoconstriction and vascular proliferation and remodeling (Fig. 1).

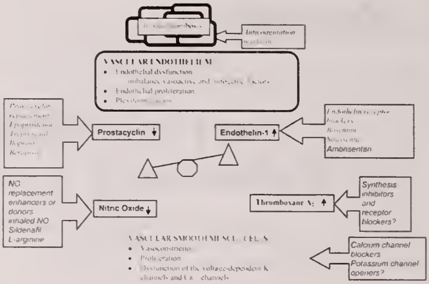
In situ thrombosis
Anticoagulation medication
VASCULAR ENDOTHELIUM
Endothelial dysfunction
imbalance vasoactive and mitogenic factors
Endothelial proliferation
Plexiform lesions
Prostacyclin replacement
Epoprostenol
Treprostinil
Iloprost
Beraprost
Prostacyclin ↓
Endothelin-1 ↑
Endothelin receptor blockers
Bosentan
Sitaxsentan
Ambrisentan
NO replacement enhancers or donors
inhaled NO
Sildenafil
L-arginine
Nitric Oxide ↓
Thromboxane A2 ↑
Synthesis inhibitors and receptor blockers?
VASCULAR SMOOTH MUSCLE CELLS
Vasoconstriction
Proliferation
Dysfunction of the voltage-dependent K channels and Ca channels
Calcium channel blockers
Potassium channel openers?

Fig. 1. Specific therapy for pulmonary hypertension is directed at excessive production of endothelium-derived vasoconstrictors and proliferative factors, such as endothelin-1, and reduced production of substances with beneficial vasodilatory properties, such as prostacyclin and nitric oxide.

Therapeutic choices in pulmonary hypertension depend on the etiology of the disease, the severity of functional impairment and the presence or absence of acute vasoreactivity at right heart catheterization. The only agents currently FDA-approved for the specific treatment of PAH are continuous intravenous epoprostenol (prostacyclin, prostaglandin I_2, Flolan®), continuous subcutaneous treprostinil (prostacyclin analogue, Remodulin®) and oral bosentan (dual endothelin receptor antagonist, Tracleer®) (12–26). Other drugs recently investigated or currently being studied in clinical trials of PAH include inhaled iloprost, oral beraprost, oral sildenafil, inhaled nitric oxide, oral L-arginine, thromboxane synthetase inhibitors and selective endothelin receptor antagonists, such as sitaxsentan (27–43). A very small group of patients who demonstrate true acute vasoreactivity at right heart catheterization may be chronically treated with oral calcium channel blockers (44–47). In addition, most patients with PH receive conventional heart failure treatment, represented by anticoagulants, diuretics, inotropic medication and oxygen supplementation (45, 48, 49) if necessary.

Recent trends in the comprehensive management of patients with PAH focus on the introduction of new drugs with different intracellular mechanisms of action or alternative routes of administration, and on the use of combination therapy for cases unresponsive to monotherapy. The currently available therapeutic options have been clearly shown to improve outcome and survival. However, the invasive nature of follow-up evaluation by right heart catheterization has created major challenges for the design of therapeutic trials in PAH because of potential ethical and logistical dilemmas. Ethical difficulties may arise from enrolling patients in double-blind, placebo-controlled, randomized studies and from establishing endpoints of death and survival. A widely used clinical endpoint for many evidence-based trials is the time to clinical worsening, defined as a composite of death, transplant or need for rescue (by intravenous epoprostenol) from the time the investigational treatment was initiated. Use of follow-up right heart catheterization to document treatment effect, although objective and accurate, may jeopardize the safety of study participants and unduly increase the cost of investigation. Recent trials are focusing more on

TABLE 2
Functional Assessement and Prognosis

Functional Class	Description	Median Survival (months)
WHO class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.	58.6
WHO class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.	58.6
WHO class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.	31.5
WHO class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.	6

Adapted from the Executive Summary — World Symposium on PPH 1998 (1).

clinically relevant endpoints, such as improvement in the 6-minute walk test (6MWT) distance or in symptoms (Borg score) and in the general clinical status (such as dyspnea-fatigue rating) (15, 21, 24–27). In particular, the 6MWT, if performed in accordance with published guidelines (50), is a relatively objective, reliable and clinically meaningful measure of outcome. In deciding the type of treatment, it is important to evaluate the baseline prognostic factors of clinical outcome. These factors include hemodynamic parameters of right ventricular function, extent of symptoms as assessed by the WHO functional class, and overall exercise capacity. Right atrial pressure greater than 15–20 mm Hg and cardiac index less than 2 L/min/m^2 obtained at right heart catheterization are associated with increased mortality. Depending on the degree of physical limitation by symptoms, the functional level of patients with PH is graded from I to IV, with higher grades indicating more severe disease and worse prognosis (1) (Table 2). This is known as the WHO functional classification and represents an adaptation of the NYHA functional classification in congestive heart failure. Distance walked during 6 minutes is an accurate and reproducible indicator of the overall exercise capacity. The distance and degree of oxygen desaturation during the 6-minute walk test correlate with prognosis and survival in patients with primary pulmonary hypertension (51, 52).

Specific Therapy for Pulmonary Artery Hypertension

Epoprostenol

Epoprostenol (Flolan®, prostacyclin, prostaglandin I_2) was approved in 1995 for the treatment of patients with PPH and PAH related to connective tissue disease. Prostacyclin (epoprostenol), a metabolite of arachidonic acid, is produced primarily in the vascular endothelium, induces direct vasodilatation of both pulmonary and systemic arterial vascular beds, inhibits platelet aggregation and increases cardiac output. In addition to direct pulmonary vasodilatation, prostacyclin probably has a chronic remodeling effect in the pulmonary vasculature; in long-term therapy, both mean pulmonary arterial pressure and pulmonary vascular resistance decrease substantially more than they do during acute testing in the catheterization laboratory (12). The long-term beneficial effect of prostacyclin in PH is probably related to a combination of these pharmacologic properties.

Prostacyclin, the most effective therapeutic agent currently available, is used for patients with World Health Organization (WHO) class III and IV and it is the only option available for patients with class IV and severe right ventricular dysfunction. For patients with PPH and most other forms of PAH, prostacyclin improves exercise capacity, pulmonary hemodynamics, right ventricular function and survival rate (12–23). Earlier studies of patients with PPH, comparing the effect of intravenous prostacyclin therapy with conventional treatment over 8 – 12 weeks, have showed significant improvement in hemodynamics and exercise capacity, which were sustained in long-term follow-up at 6 and 18 months (13 – 15). When the 6-minute walk test was used to gauge the prostacyclin effect on exercise capacity, PPH patients treated with prostacyclin had an improvement in the median walk distance of 47 m at 12 weeks and could walk over 100 m farther at both 6 and 18 months, while patients receiving conventional therapy had both hemodynamic and functional deterioration (13 – 15). For patients with PPH treated with intravenous prostacyclin, the clinical and functional improvements were associated with a survival benefit, when compared with historical controls from NIH data (14, 17). Recent studies evaluating the long-term outcome of prostacyclin treatment have documented symptomatic, hemodynamic and survival benefits for patients with PPH and other types of PAH (18 – 20). Clinical response to long-term prostacyclin therapy is predicted by the age at onset of the disease, the presence of acute vasoreactivity, the level of functional impairment as determined by WHO functional class, exercise capacity or history of right heart failure either at baseline or follow-up, and the etiology of PAH (18 – 20). Younger PPH patients with less functional impairment and good hemodynamic and clinical response at follow-up have better outcomes from long-term prostacyclin therapy (18 – 20). Decision for lung transplant referral is influenced by clinical and hemodynamic response after 3 – 12 months of epoprostenol therapy (18 – 20). Transition from intravenous prostacyclin to either subcutaneous treprostinil or oral bosentan is feasible and safe. Such transition may be a treatment alternative for stable patients or in cases of intolerable or life-threatening adverse effects from epoprostenol (53 – 56).

Prostacyclin has a short half-life (1 – 2 minutes) and requires a complicated delivery system and continuous intravenous administration. Once reconstituted for infusion, prostacyclin is unstable at room temperature and has to be preserved with ice packs. Moreover, this form of treatment requires placement of permanent central venous access, which is cumbersome and carries the risk of catheter-related infection (with a rate of 0.22 –0.68 per patient per year of local central line infection and 0.39 per patient per year of bacteremia) and thrombosis (57). The drug is delivered using a battery-operated pump. Pump malfunctioning or catheter dislocation may result in life-threatening complications from rebound pulmonary hypertension, with acute worsening of right heart failure, syncope and sudden death. Other adverse effects of prostacyclin, probably a consequence of prostaglandin excess, are headache, nausea, diarrhea, rashes, pruritus, jaw pain (usually occurring during the first bite of a meal), neuropathic pain, hypotension, dizziness and vasodilatation. Other chronic side-effects described for patients receiving chronic prostacyclin therapy are thrombocytopenia, weight loss and ascites. Currently, there is no uniform consensus regarding the exact dosing regimen of prostacyclin. In most centers, however, treatment starts with initial doses of 2 – 4 ng/kg/min. Afterwards, the dose is increased by 1 ng/kg/min each week depending on the clinical response and prostacyclin-associated adverse effects, until a total dose of about 20 ng/kg/min is reached, or until repeat right heart catheterization is performed. Studies have showed that a follow-up right heart catheterization is required 3 – 12 months after initiation of therapy for prognostic purposes, dose adjustments and further management recommendations such as listing for lung transplantation (18 – 20). Soon after the introduction of this form of therapy, it seemed that a degree of tolerance to the beneficial effect of prostacyclin develops, which leads to rapid dose escalation. Excessive doses of prostacyclin, however, have deleterious effects on the right heart function, with induction of a hyperdynamic and high output state (58). Dosing of prostacyclin is tailored to keep cardiac index above 2 L/min/m^2, but below 4 L/min/m^2, and to minimize adverse effects.

Treprostinil

Treprostinil (Remodulin®), a longer acting prostacyclin analogue, was approved in 2002 for treatment of PAH patients with WHO class II-IV symptoms. Treprostinil has pulmonary vasodilatory and antithrombotic properties. *In vitro* studies have also showed a potent antiproliferative and remodeling pulmonary vascular effect. Treprostinil has prolonged bioavailability (3-hour half-life), is stable at room temperature, and is administered by continuous subcutaneous infusion through a battery-operated pump similar to that used for insulin administration. Recent placebo-controlled trials of treprostinil administration for 8 – 12 weeks in patients with PAH have documented improvement in exercise capacity, symptoms and hemodynamics (24, 59). Exercise capacity was evaluated by the change in the mean 6-minute walk distance, with an overall treatment effect of 36 meters in a pilot study which included only patients in WHO functional classes III and IV, and 16 meters in a larger study which evaluated 470 patients with PAH in WHO functional classes II–IV (24, 55). Clinical efficacy of treprostinil is more pronounced in patients with more severe disease, as judged by lower 6-minute walk distance, higher WHO functional class and reduced mixed venous oxygenation (24, 59). Patients who were in WHO functional class IV at study entry had an average treatment effect of 54 meters (59).

In addition, the effect of treprostinil on the exercise capacity is dose-dependent, although dose escalation may be hampered by development of pain and reactions at the infusion site, as proved by the average dose of 9.3 mg/kg/min at 12 weeks instead of 22.5 ng/kg/min allowed by the study design. Ability to reach a dose of about 14 ng/kg/min after 12 weeks of treatment was associated with a mean improvement in the 6-minute walk distance of 36 meters (24). Retrospective data suggest survival advantage in PAH patients treated with treprostinil compared to expected survival from the NIH predictive equation (60).

Most common adverse events encountered in more than 80% of treated patients, are pain and reactions at the infusion site, requiring drug interruption in about 15% of cases (24, 59). Various pain management strategies have been developed to control adverse effects at the infusion site, including the local administration of pluronic lecithin organogel (PLO gel), which has been shown to provide symptomatic relief and reduce healing time over a one-month period (61). Adverse effects reflecting prostacyclin excess have been also described with treprostinil. Although complications related to malfunction of pump or infusion set are frequent, these problems are easily resolved by the patients themselves and usually result in adverse effects rated as mild to moderate in severity; no fatalities have been reported (24, 59).

Recommended initial dose of subcutaneous treprostinil is 1.25 ng/kg/min, with increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on the clinical response and severity of adverse effects. A small European study has demonstrated that rapid dose escalation to reach a target dose of 10 – 15 ng/kg/min within 2 – 3 weeks is safe and effective, and does not increase the frequency of local pain and adverse reactions (62). Transition from intravenous prostacyclin to subcutaneous treprostinil is feasible and safe, and may be warranted in cases of intolerable or life-threatening adverse effects from prostacyclin (53). A phase IV trial of treatment transition from intravenous prostacyclin to subcutaneous treprostinil is currently ongoing.

Bosentan

Bosentan (Tracleer®), a dual endothelin receptor antagonist, is the first oral agent specifically approved by the FDA (in 2001) for the treatment of PAH patients with WHO class III–IV symptoms. It represents an entirely new class of drugs in the therapeutic armamentarium of patients with PAH. Endothelin-1 is a potent vasoconstrictor, a vascular growth factor and a neurohormonal activator. Endothelin system activation is common to most forms of pulmonary vascular disease. In animal models and *in vitro* studies, endothelin receptor blockade has been associated with pulmonary vasodilatory and vascular remodeling effects and improvement in the right ventricular pathophysiologic consequences. In two randomized, double-blind, placebo-controlled clinical trials of patients with PAH, bosentan administration was associated with improved exercise capacity, symptoms and hemodynamics, and increase in the time to clinical worsening (25, 26). Clinical benefit was evident at 4 – 8 weeks and sustained at 20 weeks or more (25, 26). In the 12-week pilot study, which included 32 patients with PAH in WHO functional class III, bosentan treatment effect, as judged by the change in the mean 6-minute walk distance, was 76 meters (25). In the larger study, which included 213 PAH patients in WHO classes III and IV, treatment effect of bosentan was 44 meters at 16 weeks (26). Most favorable therapeutic benefit from bosentan is derived for patients with PPH compared to patients with scleroderma spectrum of disease (26). An open-label extension to the 12-week pilot study has shown that the improvement in exercise capacity was sustained for an additional 6 months. In addition, one year treatment with Bosentan is associated with persistent reduction in pulmonary vascular resistance and increasing cardiac index (63).

Furthermore, long-term bosentan therapy has been shown to have a positive effect on echocardiographically determined parameters of pulmonary hypertension and right ventricular dysfunction for patients with PAH (64). Retrospective data from patients who were treated with bosentan and followed up for 26 months demonstrated improved survival compared to historical controls (65). Oral administration of bosentan probably has a positive effect on the quality of life of patients with pulmonary hypertension, due to ease of administration, and it is sometimes the only viable therapeutic option for patients ineligible for prostacyclin treatment.

Bosentan administration was associated with dose-related liver injury in 10–11% of study patients (25, 26). Liver injury is manifested by elevation in the hepatic aminotransferase levels, which is reversible upon dose reduction or treatment discontinuation. Mechanism of aminotransferase increase is uncertain, but it may result from competitive inhibition of bile salt elimination from hepatocytes. During bosentan therapy, liver enzymes must be monitored on a regular basis, and dose adjustments made or treatment discontinuation guidelines followed in cases of detected abnormalities. To date, no fatalities secondary to liver insult have been reported (personal communication, Actelion). Nevertheless, initiation of bosentan therapy in patients with pre-existing liver disease is not recommended. Bosentan has teratogenic potential and is contraindicated in pregnancy. Other adverse effects reported with bosentan include headache, nasopharyngitis, flushing, lower extremity edema, hypotension, palpitations, dyspepsia, fatigue and pruritus. Lower extremity edema may be a local phenomenon and not a reflection of worsening in the right ventricular function, and may be readily reversible with diuretics. Bosentan treatment is initiated after baseline liver function test is performed, at a 62.5 mg bid oral dose for one month. After one month, if the aminotransferase levels are stable, dose is increased to 125 mg po bid, which has the most favorable risk-benefit ratio. Clinical trials have suggested that a 250 mg po bid dose is more efficacious in improving exercise capacity of bosentan-treated patients, but the incidence of adverse effects increased as well (26). Therapeutic efficacy of bosentan treatment is evaluated by patients' symptoms and by periodic 6-minute walk test performance, with repeat right heart catheterization every 6–12 months or as dictated by the clinical status. In the absence of a favorable clinical and hemodynamic response, transition to intravenous epoprostenol may be considered. Administration of bosentan in combination with intravenous prostacyclin or subcutaneous treprostinil appears safe and, in certain cases, allows transition from parenteral prostacyclin therapy to oral treatment (54–56).

Treatment of Other Forms of Pulmonary Arterial Hypertension

Connective Tissue Disease

Development of pulmonary hypertension in various connective tissue disorders is associated with increased morbidity and mortality. PAH in connective tissue diseases is often an isolated phenomenon, which bears pathogenetic or management similarity with PPH. In other cases, however, PH appears as a consequence of other pulmonary pathologic processes such as pulmonary fibrosis or chronic thromboembolism. A large multicenter, randomized, placebo-controlled trial of prostacyclin treatment for patients with the scleroderma spectrum of disease has demonstrated symptomatic, functional and hemodynamic benefit from prostacyclin administration at 12 weeks, compared with conventional therapy (21). The difference between the treatment groups in the median 6-minute walk distance was 108 meters (21). Beneficial use of prostacyclin has been demonstrated in PAH associated with other forms of connective tissue disease, such as systemic lupus erythematosus (66, 67). Multicenter randomized trials of treprostinil and bosentan included patients with PAH associated with connective tissue disease. Group subset analyses showed that specific treatment of pulmonary hypertension is less effective in both short-term and long-term follow-up for patients with connective tissue disease PAH compared to PPH, while most benefit is derived from apparent halting of the disease progression (26).

End-Stage Liver Disease

Presence of portopulmonary hypertension increases morbidity and mortality of patients with end-stage liver disease and has an important impact on their eligibility for liver transplantation. Patients with moderate-to-severe pulmonary hypertension have unacceptably high perioperative mortality. Evidence exists for favorable hemodynamic response to chronic prostacyclin therapy, which can be used perioperatively to decrease pulmonary pressure and improve right ventricular function (68, 69). Chronic intravenous prostacyclin therapy may also decrease cardiovascular mortality of patients with portopulmonary hypertension (69). A side effect of prostacyclin therapy often found in patients with portopulmonary hypertension is thrombocytopenia, probably from hypersplenism or immune causes (70). There are reports of the safe use of treprostinil by patients with portopulmonary hypertension, and in the near future, treprostinil may become a suitable alternative for patients who are not prostacyclin candidates (71). Bosentan is not recommended for patients with severe liver disease.

HIV Infection

In HIV-related pulmonary hypertension, viral infection and secondary inflammation may have a direct or indirect effect on pulmonary vessels. In a small-series study of patients with HIV-related PAH, intravenous prostacyclin therapy has been associated with symptomatic and hemodynamic benefit (72, 73). A recently published case series of patients with HIV-associated PAH has demonstrated that continuous intravenous prostacyclin and highly active antiretroviral therapies were independent predictors of improved survival (74).

Congenital Heart Disease

In a series of patients with congenital heart disease unresponsive to conventional therapy, long-term administration of intravenous prostacyclin induced hemodynamic, symptomatic and functional improvement at one year (75).

Oral Calcium Channel Blockers

Chronic administration of oral calcium channel blockers (OCCB) is beneficial in fewer than 10% of PPH patients who demonstrate acute vasoreactivity during testing in the catheterization laboratory with short-acting agents, such as inhaled NO, and intravenous adenosine or prostacyclin. Patients with true acute vasoreactive response demonstrate a substantial reduction in the mean pulmonary artery pressure of more than 10 mm Hg to reach a level lower than 40 mm Hg, in the absence of a significant decrease in the cardiac output or systemic arterial pressure (47). Initiation of OCCB therapy must be undertaken under close hemodynamic monitoring until the highest dose devoid of adverse effects is reached (46). This restricted group of patients, who respond acutely to pulmonary vasodilators, derive long-term hemodynamic and survival benefit from OCCB treatment (44, 45, 47). Patient selection and long-term monitoring for both safety and efficacy represent a challenging aspect in the management of patients with PH, since indiscriminate use of OCCB may result in worsening right heart failure and death. Patients who initially respond to OCCB therapy but subsequently develop disease progression should be treated with alternative agents, and OCCB should be discontinued. There are no available large-scale studies of OCCB treatment in PAH other than PPH.

Combination Therapy for PAH

Since multiple and complex pathogenetic mechanisms are implicated in the development and progression of pulmonary arterial hypertension, it is possible that treatment combining various classes of vasodilator drugs will be used for those PAH patients who are refractory to the standard treatment protocol. Prostacyclins, endothelin-receptor antagonists and drugs acting through a NO-dependent pathway (such as sildenafil, a phosphodiesterase inhibitor) have different intracellular signal transduction pathways, with multiple cross-talk mechanisms that may have synergistic beneficial effects in the treatment of PAH. There is evidence from *in vitro* and animal studies that combining classes of drugs with different mechanism of action enhances the effect on the pulmonary vasculature. Although small human clinical trials on various combinations of drugs effective in PAH management have been reported (54–56), at the present time, the absence of efficacy and safety data in large clinical trials precludes the widespread recommendation of combination PAH therapy as an initial treatment approach. Preliminary results from a 12-week multicenter clinical trial on the combined use of prostacyclin and bosentan initiated simultaneously have demonstrated that the combination is well tolerated and that bosentan may provide a small additional benefit to patients with severe PAH who require prostacyclin treatment (54). In retrospective studies of PAH patients chronically treated with either prostacyclin or treprostinil, subsequent addition of bosentan was safe and effective, allowing for prostacyclin dose reduction or even discontinuation (55).

Small series from other countries have demonstrated acute and chronic benefit from combined use of various investigational drugs for PAH, such as inhaled iloprost, a long-acting prostacyclin analogue, inhaled NO and oral sildenafil or from addition of sildenafil for patients with suboptimal response to chronic prostacyclin (76–81).

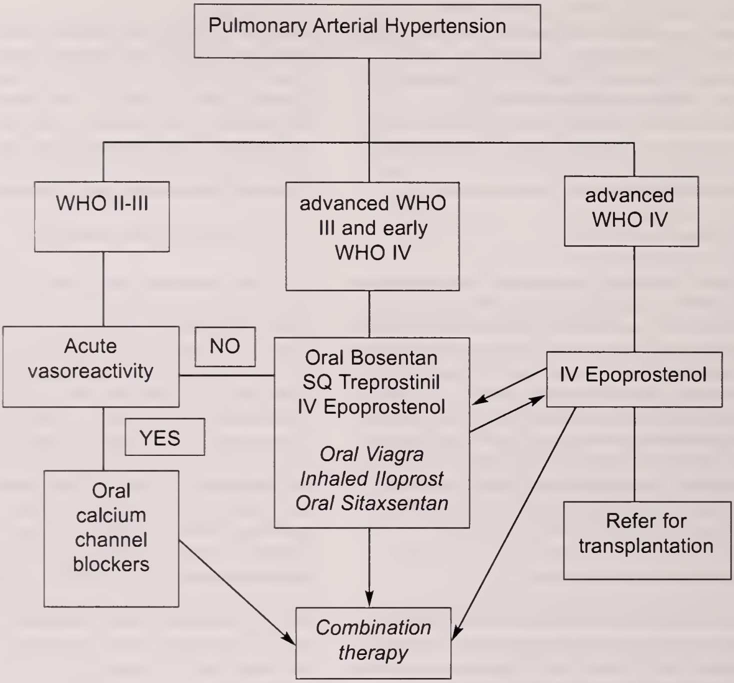
Pulmonary Arterial Hypertension
WHO II-III
advanced WHO III and early WHO IV
advanced WHO IV
Acute vasoreactivity
NO
YES
Oral Bosentan
SQ Treprostinil
IV Epoprostenol
Oral Viagra
Inhaled Iloprost
Oral Sitaxsentan
IV Epoprostenol
Oral calcium channel blockers
Refer for transplantation
Combination therapy

Fig. 2. For patients with early disease and positive acute vasodilatory response, a trial of oral calcium channel blockers is indicated. For most patients who do not respond acutely to vasodilator challenge, treatment depends on the WHO functional class. Most appropriate treatment strategy for patients with WHO I and II class symptoms is not yet determined. Endothelin receptor antagonist bosentan and prostanoids, such as treprostinil and epoprostenol, are indicated for patients in WHO functional class III and stable patients in class IV. The only option for severely ill patients or patients with rapidly progressive disease in the WHO functional class IV is intravenous epoprostenol. Selective ET_A receptor antagonists, prostanoids with alternate route of administration and different classes of drugs are currently investigated. Combination therapy may be considered in case of no improvement or deterioration with primary treatment.

Conventional Therapy

Anticoagulant Therapy

Treatment with warfarin has been associated with improved survival in retrospective and prospective studies of patients with PPH (45, 49). Survival benefit was most pronounced for patients unresponsive to OCCB (45). Likely benefit from anticoagulation in PAH is related to the effect on the *in-situ* thrombosis and possibly occurs by counteracting the effects of thrombin activation (80) in the pulmonary vascular bed. In the absence of contraindications, anticoagulation is recommended for all patients with PH. The goal of warfarin therapy in PAH is to keep INR between 2 and 3 (83).

Diuretics

Diuretics are used to reduce the fluid overload state, a condition commonly encountered in patients with PAH and right ventricular failure. Hemodynamic optimization in these cases requires reduction in peripheral edema, ascites and hepatic congestion, with the goal of keeping the fluid balance slightly on the dry side, but without compromising right ventricular filling. Diuretic combinations or intravenous agents may be necessary in refractory cases.

Inotropes

Digoxin may be used in cases of right ventricular dysfunction; however, its long-term benefit is uncertain. A short-term study of a few patients with PPH demonstrated that digoxin increases the cardiac output and reduces neurohormonal activation (48).

Supplemental Oxygen

Home oxygen therapy is recommended for patients who develop hypoxemia at rest, with exercise or during sleep, with the goal of keeping O_2 saturation above 90–92%, to reduce any potential component of hypoxic vasoconstriction.

Treatment Algorithm for Pulmonary Arterial Hypertension

Factors that influence treatment decisions for patients with PAH include the etiology of the disease, the presence or absence of acute vascular reactivity during right heart catheterization, and the degree of functional impairment. The treatment algorithm for PAH has undergone major modifications in the past year, to include the agents newly approved by the FDA (Fig. 2), and further changes are expected in the near future to reflect the continuous expansion of the therapeutic armamentarium for pulmonary hypertension.

For patients with early disease in WHO classes I–II and selected, clinically stable patients in class III in whom acute vasoreactivity has been demonstrated in the laboratory, a trial of oral calcium channel blocker therapy under close hemodynamic monitoring is indicated. Until recently, intravenous epoprostenol was the first-line treatment for PAH patients with WHO class III and IV symptoms who were unresponsive to the acute vasodilator trial. Currently, in the absence of acute vasoreactivity, initial therapy for WHO class III and stable WHO class IV patients consists of subcutaneous treprostinil or oral bosentan. Treprostinil is the only FDA-approved agent for patients with WHO class II symptoms and no acute vasodilator responsiveness. Intravenous prostacyclin is still considered the most effective therapeutic option available and is reserved for patients in WHO class IV with severe functional impairment and for patients who fail treprostinil or bosentan therapy. Selected patients who are stable on intravenous epoprostenol or who develop complications related to intravenous treatment may be transitioned to other forms of therapy, such as subcutaneous treprostinil or oral bosentan. Combination therapy and use of investigational agents such as inhaled iloprost or orally administered sildenafil and sitaxsentan are promising treatment options that need further validation.

Conclusion

There has been significant progress in the treatment of pulmonary hypertension in the past decade. Intravenous prostacyclin has been the standard for treatment of patients with advanced disease. However, the risks associated with this intravenous treatment have limited its popularity and clinical usefulness. The advent of the oral endothelin-receptor antagonist has dramatically altered the treatment options available to patients with less advanced symptoms. The introduction of the subcutaneous form of the longer-acting prostacyclin analogue allows greater treatment flexibility. Treatment of pulmonary hypertension has evolved from adopting the standard treatment regimen of congestive heart failure to the current use of selective pulmonary vasodilators and growth inhibitors. Future advances in the understanding of the genetic and molecular basis of this elusive disease will provide new hope for a cure.

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Neurohormonal Antagonism in Heart Failure:

What Is the Optimal Strategy?

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Abstract

Pharmacologic management of chronic heart failure rests on appropriate volume management followed by neurohormonal antagonism. Despite the rationale for neurohormonal antagonists, their use remains low.

Definitive studies establish that neurohormonal antagonists are effective across the spectrum of disease, from the early Stage A patient at risk of developing structural heart disease and symptomatic heart failure to the Stage D patient with symptoms at rest.

Although many investigators and clinicians seem focused on the next new scientific breakthrough, published studies delineate strategies that will reduce death and disability for those at risk and those with symptomatic chronic heart failure. In essence, the broad use of neurohormonal antagonists, consistent with the reports of large-scale trials that have been reported, will markedly reduce the risk of disease progression and death. Overall prognosis however remains poor.

We review the data from these trials to encourage clinicians to use these proven neurohormonal antagonists in optimizing therapeutic strategy.

Key Words: Chronic heart failure, neurohormonal antagonism, treatment.

Introduction

CHRONIC HEART FAILURE is classically described as a clinical syndrome in which abnormalities of left ventricular (LV) function and neurohormonal regulation lead to progressive functional limitation, fluid retention, and increased risk of death. Coronary artery disease and hypertension are the two most common triggers leading to the development of heart failure, with subsequent activation of neurohormonal systems leading to progression to the symptomatic stage of heart failure (1). The role of these neurohormonal systems is well described; although serving an important role in maintaining circulatory homeostasis in the short term, chronic activation is toxic to the myocardium — worsening hemodynamic and clinical status (2).

Over the past two decades, numerous studies have demonstrated that neurohormonal antagonists slow the progression of heart failure, improving symptoms and reducing the risk of death (3 – 14). Therefore, patients with heart failure should receive at least two neurohormonal antagonists, angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Recent data suggests potential utility for an additional class of neurohormonal antagonist, the angiotensin receptor blockers (ARB) (15, 16). However, recent studies suggest a potentially adverse interaction when additional neurohormonal antagonists are used in conjunction with ACE inhibitors and β-blockers (16, 17). This observation is not unique to this angiotensin receptor blocker, as centrally acting sympatholytic moxonidine was associated with increased risk of death and the β-blocker bucindolol could not better placebo in a large-term, adequately powered clinical trial (13, 18, 19). In general, drug development programs have focused on antagonizing deleterious neurohormones (and cytokines). Yet such agents directed against endothelin proved risky (20), and cy-

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tokine antagonists offer no benefit (21). In contrast, aldosterone inhibitors appear promising (22, 23). In patients with left ventricular dysfunction and heart failure after a myocardial infarction, eplerenone, an aldosterone inhibitor, reduces the risk of death and major morbidity (23).

A major problem is that the standard definition of heart failure focuses on patients whose disease has advanced to the symptomatic phase, while the disease process leading up to this point includes far greater numbers of patients; those who are at risk of developing overt heart failure and are at risk of sudden death. Accordingly, the recent AHA/ACC guidelines focus attention on this larger population of patients at risk, specifically those with coronary disease, hypertension, dyslipidemia and diabetes by introducing a new classification system for heart failure (24). These four stages of heart failure, and the recognized progressive course for those who are at risk reinforce the importance of determining the optimal strategy for neurohormonal antagonism as we attempt to improve the natural history of the syndrome (Table 1). Our purpose is to review the effects of the available neurohormonal antagonists in order to propose a strategy for optimal neurohormonal antagonism.

TABLE 1
Stages of Heart Failure, Adapted from AHA/ACC Guidelines (24)

Stage	Description	NYHA	Clinical Clues
A	Patients at high risk of developing HF.	Not applicable	Coronary artery disease, hypertension, diabetes, dyslipidemia, family history of cardiomyopathy.
B	Patients who have structural heart disease but have never manifested signs or symptoms of HF.	I	Left ventricular hypertrophy (by ECG or echo), valvular disease, past myocardial infarction.
C	Patients who have current or prior symptoms of HF.	II–III	Dyspnea, fatigue, exercise intolerance, prior HF hospitalization.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest.	IV	End-stage, awaiting transplant, receiving palliative care.

Adrenergic Antagonists

Clinical Trials

There is no longer doubt that adrenergic antagonism is standard care for patients with heart failure. β-blockers reduce symptoms, slow disease progression and decrease the risk of death (8, 9, 13, 25, 26). β-blockers are effective for patients with heart failure due to ischemic or non-ischemic etiologies (8, 9, 26), and improve outcomes whether patients are minimally symptomatic or suffer from advanced disease (8, 9, 13, 14, 25, 26). However, not all agents that antagonize the sympathetic nervous system (SNS) have the same effects (13, 18, 19). Therefore, one cannot assume that all adrenergic antagonists are interchangeable for the treatment of heart failure, and in our climate of evidence based medicine, we should select the agents proven to be effective in randomized controlled clinical trials. The β-blockers that are currently available differ in their specificity for β-1 and β-2 receptors, with some (e.g., metoprolol and bisoprolol) considered relatively β-1 receptor selective while others (e.g., carvedilol) are relatively non-selective. Recent data suggests that metoprolol may be less β-1 selective than previously considered. In a controlled trial comparing carvedilol to metoprolol succinate, patients had doses titrated toward target, and at each visit, had an assessment of β-2 antagonism via measurement of glucose and potassium during terbutaline infusion. This study demonstrated that 100 mg of metoprolol succinate is mildly selective and 200 mg not selective at all relative to carvedilol 12.5 and 25 mg bid, respectively (27). Several β-blockers also have properties in addition to β-blockade; for example, carvedilol has α-1-blocking (vasodilator) and antioxidant properties and bucindolol also causes vasodilation, although the mechanism of this is as yet unclear. Although it is not known whether these pharmacological differences result in clinically meaningful differences between the three β-blockers proven to improve clinical outcomes in heart failure — carvedilol, metoprolol succinate and bisoprolol (Table 2) — the COMET study demonstrated significant clinical benefits from carvedilol compared with metoprolol tartrate (33).

TABLE 2
Beta-Blockers for Heart Failure

A. Beta-Blockers Proven Effective in Heart Failure

Drug	Start Dose	Target Dose	Other Indications
Carvedilol	3.125 mg BID	25–50 mg BID	HTN, post-MI LV dysfunction
Metoprolol succinate*	12.5 mg QD	200 mg QD	HTN, angina
Bisoprolol	1.25 mg QD	10 mg QD	HTN, angina

B. Beta-Blockers Used in Heart Failure Trials

Drug	Start Dose	Studied Dose	Other Indications
Metoprolol tartrate	6.25 mg BID	50 mg BID-TID	HTN, angina, acute MI

C. Beta-Blockers Not Evaluated in Large-Scale Heart Failure Trials

Drug	Indications
Atenolol	HTN, angina, acute MI
Propranolol	HTN, angina, migraine, atrial arrhythmias

HTN = hypertension, CAD = treatment of acute and/or chronic coronary disease, LVD = left ventricular dysfunction, CHF = chronic heart failure, MI= myocardial infarction. * = under FDA review for heart failure indication.

Drug Selection

Although the initial randomized studies comparing carvedilol and metoprolol were not sufficiently powered to show a clinical difference in outcome, the surrogate endpoints evaluated were intriguing (28–31). Metra and colleagues evaluated the effects on ventricular performance and exercise hemodynamics in 150 patients randomized to receive carvedilol or metoprolol for up to 44 months. When reassessed after 13–15 months of treatment, although both groups improved, the carvedilol-treated patients had significantly greater increases in LV ejection fraction at rest, and in LV stroke volume and stroke work during exercise, and also had greater decreases in mean pulmonary wedge pressure, both at rest and during exercise compared with metoprolol. In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group (31). Di Lenarda evaluated the effects of carvedilol in 30 patients who remained limited by symptoms of heart failure and ventricular dysfunction after at least 1 year of treatment with metoprolol. In this open-label study, ejection fraction improved significantly by 1 year after changing from metoprolol to carvedilol (30). In contrast, two studies that randomized patients to carvedilol or metoprolol found no differences in hemodynamics (28, 29) or measures of oxidative stress (28), although carvedilol significantly reduced left ventricular end-diastolic dimension to a greater extent (29). It should be noted that the surrogates used in these studies, however, are not necessarily predictive of clinical effects. This is even more apparent when one realizes that the adrenergic antagonist moxonidine reduces sympathetic activation (32) yet increases the risk of death (19).

Carvedilol, metoprolol and bisoprolol all improve well-being and reduce the risk of death. However, the Carvedilol or Metoprolol European Trial (COMET) allows us to be more definitive in prioritizing the utility of particular β-blockers for the treatment of heart failure. This study compared carvedilol (25 mg BID) to metoprolol tartrate (50 mg BID) and demonstrated that carvedilol reduced the risk of death significantly better than metoprolol tartrate (33). Some may find it difficult to apply these data to clinical practice, since metoprolol tartrate was studied but metoprolol succinate is the formulation proven to be effective in heart failure.

Despite the multitude of ways the data can be interpreted, a simple view may be most useful for clinical practice. Since carvedilol has proven to be better than other β-blockers, carvedilol must be viewed to be superior within its class. Perhaps another β-blocker might yet be proven to be as good or better. Therefore, based on the available data (33), all heart failure patients should be treated with carvedilol. Alternatively, since the heart rate reduction with carvedilol and metoprolol tartrate were similar over the course of the study, and therefore the drugs were dosed for comparable β1 blockade, the superiority of carvedilol may reflect the importance of β2 and α1 blockade.

Metabolic Effects

Carvedilol produces different metabolic effects than metoprolol (34) and atenolol (35), which may be of clinical relevance considering the link between insulin resistance and clinical outcomes (36–38). The mechanism of this difference appears to relate to the α-1 antagonism of carvedilol (39). If this effect were independent of the anti-hypertensive effects of these agents, then it could prove quite important, as non-diabetic patients with mild-to-moderate heart failure can be insulin resistant (40–43). The COMET trial reported a 22% reduction in the development of diabetes in patients with heart failure treated with carvedilol compared to metoprolol (p=0.04) (44), supporting the findings of these smaller mechanistic studies (34, 35).

Strategies for Clinical Practice

β-blockers should be administered to all patients with symptomatic heart failure when they are stabilized on oral medications (13, 45, 46) as well as those with left ventricular dysfunction after a myocardial infarction (14). Background therapy should include diuretics as required, digoxin and ACE inhibitors. This strategy could extend to asymptomatic patients with only mild LV dysfunction, based on the data in patients treated after a myocardial infarction (14) (stage B heart failure), the known pathophysiology of the disease (1), and the risk that the first manifestation of disease progression can be sudden death.

Patients with severe heart failure who require inotropic agents intravenously or other assist devices should be started on β-blocker therapy when weaned from intravenous medications and stabilized on oral agents (13). Starting doses of β-blockers should be as low as possible, with gradual increases over several weeks or months towards the target doses used in the large-scale trials (47). In contrast to ACE inhibitors, for which it took over 15 years of use before dose ranging trials were completed (48), we know the minimally effective dose for at least one β-blocker, carvedilol. Although this dose-ranging study with carvedilol is supportive of increasing the dose to 25 mg BID, most of the relevant endpoints were significantly improved even at the lowest dose studied, 6.25 mg BID (49). While it is tempting to conclude that any dose of any β-blocker that is hemodynamically active would be acceptable, this may not be a safe conclusion to apply to those β-blockers where dose-ranging data are not available, and therefore the lack of such data with metoprolol and bisoprolol could seem to be a problem. However, each of the drugs has been shown to be effective in clinical trials with a strategy of increasing the dose to that which is maximally tolerated, and this should be the plan in clinical practice. On average, patients tolerate the up-titration to target doses well. During this initiation phase, sicker patients are at higher risk of developing fluid retention and symptomatic hypotension if the dose is escalated rapidly, at weekly intervals (50), but the risk of these side effects is not increased when the dose is increased more gradually and in fact, risk of worsening heart failure is reduced within the first weeks of administration (51). In most patients, this is not a major problem and management of these side effects is generally successful when the rate of dose escalation is slowed and background therapies are adjusted (47). In fact, β-blockers can be safely administered to patients with symptoms at rest or with minimal exertion, as demonstrated in the Copernicus trial (13).

ACE Inhibitors

Clinical Trials

ACE inhibitors are a proven therapy for patients with ventricular dysfunction, whether symptomatic or not (3, 5–7, 52). Recent studies have supported the utility of ACE inhibitors in limiting the initial myocardial injury that leads to heart failure, both in the setting of acute myocardial infarction (53–56) and in those at risk of developing heart failure (52). The Heart Outcomes Prevention Evaluation (HOPE) study provided compelling data to use ACE inhibitors more widely. The trial assessed the role of the ACE inhibitor ramipril on cardiovascular events, survival and the development of heart failure in 9,533 patients. The population studied did not meet the "standard" criteria for ACE inhibitor therapy: their blood pressure was controlled and ventricular function was normal, yet they were at a high risk for cardiac events (being either patients with vascular disease or diabetics with at least one additional coronary risk factor). The primary endpoint of cardiovascular death and major morbidity was reduced by 22% and the risk of heart failure by 23% (52). These data mandate that

ACE inhibitors become first-line therapy for patients with vascular disease, including patients with cerebrovascular or coronary artery disease, in addition to those with the traditional coronary risk factors.

Drug Selection

The debate over potential superiority of some agents over others focuses on pharmacokinetic and pharmacodynamic differences because there are no comparative studies with outcomes data. Those agents with longer half-lives would appear to afford a dosing advantage, resulting in better patient compliance. Other agents have greater distribution into tissues, potentially affecting the local renin-angiotensin-aldosterone system (RAAS) in the vascular endothelium and myocardium. In a comparative study, a tissue binding ACE inhibitor had a significantly greater effect on peripheral arterial vasodilation compared with a non-binding agent (57). Unfortunately, there are no studies that address the clinical impact of this pharmacologic property, although the tissue binding properties of an ACE inhibitor can be quite important.

Two lines of evidence suggest advantages of tissue avidity. In sudden death and acute myocardial infarction, angiotensin II and activated immune cells co-localize to the site of plaque rupture (58). This phenomenon increases the activation of the metalloproteinases that promote plaque rupture (59). Therefore, if an ACE inhibitor could penetrate into the tissue and interrupt the production of angiotensin II, it could yield a clinical benefit. Such a benefit has not been demonstrated and is not being addressed by any ongoing trial. However, the possibility of benefit cannot be ignored. An additional advantage for a tissue avid ACE inhibitor relates to the frequency of administration. For example, ramiprilat, the active form of ramipril, has only a 2–4 hour half-life. This would suggest the need for TID dosing, except that ramiprilat has triphasic elimination kinetics, meaning that following absorption into the plasma and rapid distribution into tissues, drug clearance from the plasma is followed by release of ramiprilat from the tissues back into the circulation. This results in an effective half-life of over 50 hours (60). Therefore, even without clinical outcomes data, tissue avidity of an ACE inhibitor can be an important factor in drug selection. Agents that bind to the tissues in this fashion can realize an effective half-life long enough to be administered once daily, as would be the case with a non-tissue avid agent with a much longer half-life, such as lisinopril. It should be noted, however, that those with a longer half-life may be less likely to cause dizziness and hypotension due to their gradual onset and more constant hemodynamic effects over the course of the day. Either strategy permits once-daily dosing, which would improve patient compliance. Once an agent is chosen, the target dose is generally the maximum tolerated. However, there are no general rules that can be applied to all patients to determine when the maximum tolerated dose has been achieved, especially when blood pressure starts to drop or functional azotemia develops. The standard recommendation has been to use the doses shown to be effective in randomized clinical trials (45) (Table 3).

Recently, two large studies evaluated the clinical effects of low- compared with high-dose ACE inhibitor therapy. The NETWORK study evaluated the effects of 2.5, 5 and 10 mg BID of enalapril in 1,500 patients with chronic heart failure over 6 months. The study demonstrated no difference between the doses used in terms of all-cause mortality (61). The Assessment of Treatment with Lisinopril and Survival (ATLAS) (48) study enrolled 3,164 patients, followed for a mean of 3.5 years, comparing 2.5–5 mg daily of lisinopril with 32.5–35 mg daily. Although Atlas failed to demonstrate a difference in its primary endpoint, all-cause mortality, the 12% reduction in the combined endpoint of death and hospitalization supports the use of higher doses when tolerated. Perhaps most interestingly, patients on high-dose lisinopril tolerated the drug well and had a lower incidence of cough (48). This is likely due to improvement in cardiac filling pressures at higher doses reducing the frequency of cough caused by pulmonary hypertension and congestion. This would indicate that any patient experiencing cough with an ACE inhibitor should have the dose increased as aggressively as possible to determine whether they are able to tolerate ACE inhibition and realize its clinical benefits. If this strategy is not effective, the dose of diuretics can be increased. Doubling the dose once or even for several days can be sufficient to reduce subclinical congestion, and if weight drops and the cough still does not improve, then it becomes more likely that this is an ACE inhibitor-induced cough. Importantly, cough is common in heart failure patients, but review of clinical trials of ACE inhibitors reveals that the placebo-treated patients experience cough al-

TABLE 3

Antagonists of the Renin-Angiotensin-Aldosterone System for Heart Failure

A. Agents Proven Effective in Heart Failure and/or Left Ventricular Dysfunction

Drug	Start Dose	Target Dose	Other Indications
Captopril	6.25 mg TID	50 mg TID	HTN
Enalapril	2.5 mg BID	20 mg BID	HTN
Lisinopril	2.5 mg QD	40 mg QD	HTN
Quinapril	5 mg BID	20 mg BID	HTN
Ramipril	1.25 mg QD	10 mg QD	HTN, post-MI
Trandolapril	1 mg QD	4 mg QD	HTN, LVD post-MI
Zofenopril	7.5 mg QD	30 mg QD	HTN
Spironolactone	12.5 mg QD	25 – 50 mg QD	Ascites
Valsartan	80 mg BID	160 mg BID	HTN, HF if ACE inhibitor intolerant
Epleneronone	25 mg QD	50 mg QD	HTN, LVD post-MI

B. Agents Studied in Heart Failure But Not Proven Effective in Large-Scale Trials

Drug	Start Dose	Maximum Dose	Other Indications
Fosinopril	5 mg QD	40 mg QD	HTN
Benazepril	5 mg QD	20 mg QD	HTN
Perindopril	2 mg QD	16 mg QD	HTN
Losartan	25 mg QD	50 mg QD	HTN
Irbesartan	75 mg QD	300 mg QD	HTN
Candesartan	4 mg QD	16 mg QD	HTN

C. Agents Used Clinically But Not Evaluated in Large Scale Heart Failure Trials

Drug	Indications
Moexipril	HTN
Tasosartan	HTN
Eprosartan	HTN
Telmisartan	HTN

HTN = hypertension, CAD = treatment of acute and/or chronic coronary disease, LVD = left ventricular dysfunction, CHF = chronic heart failure, MI= myocardial infarction.

most as frequently (3, 6). Although ATLAS can be interpreted as evidence to treat patients with low doses of ACE inhibitors, many patients do feel better at higher doses. In clinical practice, we should follow the strategy from the large-scale, randomized, placebo-controlled trials that proved the effectiveness of ACE inhibitors, i.e., to titrate the dose to the maximum tolerated over several weeks. In so doing, we will be providing the maximum benefit of neurohormonal blockade.

Metabolic Effects

ACE inhibitors are also useful for correcting metabolic abnormalities in heart failure patients. Insulin resistance diminishes following the administration of ACE inhibitors (62 – 64), this is important in heart failure patients because of the tendency for diuretics to worsen insulin resistance (63 – 65). This corrective effect occurs independently of angiotensin II activity, and may represent an advantage of ACE inhibitors over angiotensin receptor blockers (62, 66). Additionally, ACE inhibitors reduce proteinuria (67), and slow the progression to renal failure for hypertensives — a common comorbidity in heart failure patients. Recent trials with the angiotensin receptor blockers losartan (68) and irbesartan (69) demonstrate similar effects in type 2 diabetics, indicating that the mechanism relates in large part to antagonism of angiotensin II.

Strategies for Clinical Practice

Treatment guidelines for the use of ACE inhibitors in clinical practice describe starting doses, target doses, and the side effects (45, 46). Two factors that often lead to inappropriate drug withdrawal deserve particular attention. First, modest azotemia should not necessarily indicate impending renal failure or the presence of significant renal artery stenosis. As angiotensin II vasoconstricts the efferent arteriole in the glomerulus, a reduction in the amount of angiotensin II produced through ACE inhibition or angiotensin receptor blockade should decrease glomerular filtration, leading to "functional" azotemia (70). In this case, a slight rise in creatinine of 0.2–0.5 mg/dL should be accepted if it remains stable thereafter. The level of tolerance becomes less in patients with a baseline creatinine above 2.0 and even less above 2.5 mg/dL. If creatinine level becomes markedly elevated, the diagnosis of renal artery stenosis should be pursued. Second, lack of a therapeutic benefit after only a few days or weeks should not lead to drug withdrawal, as these agents produce short-term effects that may vary greatly from their long-term effects (71), and they may not produce clinically measurable effects for up to 3 months (72). Additionally, these agents can prevent progression of disease and reduce the risk of death, even in the absence of improved quality of life (3). Patients more likely to experience side effects early in treatment can be identified; e.g., sicker patients with hyponatremia (73), diabetics (74), those with marked renal dysfunction (75), or those with marked activation of the RAAS, including patients who have recently undergone a large volume diuresis. Those patients with low right atrial pressures (≤ 12 mm Hg) and preserved renal function (<1.5 mg/dL) appear twice as likely to improve clinically than those with high right atrial pressure and abnormal serum creatinine levels (76).

Angiotensin Receptor Antagonists

Rationale

In contrast to ACE inhibitor therapy, which prevents the adverse effects of angiotensin II by blocking its synthesis via ACE, angiotensin receptor blockers prevent angiotensin II from acting on the cell by selectively blocking AT_1 receptors. This prevents vasoconstriction, sodium retention, hypertrophy, and fibrosis. Additionally, the effects of angiotensin II as a positive inotrope and a stimulus for the secretion of endothelin and the release of norepinephrine would be blocked (77). Angiotensin receptor blockade effectively treats hypertension and improves cardiac filling pressures in patients with heart failure (78, 79). Since angiotensin II can be produced by enzymatic pathways in addition to the ACE pathway (77), levels of angiotensin II begin to rise months or years after starting therapy with an ACE inhibitor (80, 81). Therefore, angiotensin receptor blockers may be a more direct approach to blocking the effects of RAAS system activation in patients with heart failure.

Clinical Trials

Angiotensin receptor blockers initially were evaluated as an alternative to ACE inhibitors for patients with heart failure, based upon the expectation that they would prove as effective with less azotemia and a lower incidence of cough. While the hemodynamic effects were similar to that seen with ACE inhibitors, the Evaluation of Losartan in the Elderly (ELITE I) trial was the first study to address the clinical impact of these agents. This study appeared to show a reduction in the risk of sudden death with losartan compared with captopril, but the study was not definitive, as this analysis was a secondary endpoint for which the statistical power was not very robust (82). A second trial, ELITE II, attempted to confirm the observation, but the results appeared to favor the ACE inhibitor, although the differences did not reach statistical significance (83). The investigators concluded that, of the two classes, ACE inhibitors remain the therapy of choice. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study, candesartan was evaluated relative to enalapril and the combination. This study was not designed to assess the effect on clinical endpoints, but rather on neurohormonal activation and LV remodeling. However, patients who received angiotensin receptor blockers did not appear to respond as well as those on enalapril alone, although there were no significant differences (17). These trials did not address an equally important issue, that of whether angiotensin receptor blockers are useful when added to ACE inhibitor therapy.

Two trials were designed to assess the safety and efficacy of combined ACE inhibitor and angiotensin receptor blocker therapy in chronic heart failure, Val-HeFT, the recently completed study using valsartan (16) and Charm, which recently reported its results (84). The results of Val-HeFT support the use of this angiotensin receptor blocker in patients with chronic heart failure who are intolerant of ACE inhibitors (44% reduction in the combined risk of death or hospitalization), but raise questions about the addition of this therapy in patients already receiving ACE inhibitors and β-blockers.

For these patients, the addition of valsartan was associated with a trend toward increased risk of death or hospitalization (RR = 1.18, p = ns) and a trend towards higher risk of death (RR = 1.41, p = ns) (16). Although these estimates cannot be considered definitive, due to the nature of subgroup analyses and the level of statistical significance, the trends are strong enough to warrant restraint when considering combination therapy with β-blockers, ACE inhibitors and ARBs, in particular when the ARB is valsartan. Such perspective may be judicious based on the contrasting finding of safety using candesartan in combination with β-blockers and ACE inhibitors, as reported in the CHARM study (84). Candesartan was associated with a strong trend toward reduction in the risk of death (0.91, 95% confidence intervals 0.83 – 1.00, p=0.55) along with significant decrease in the risk of cardiovascular death (0.88, 95% CI 0.79–0.97, p=0.012) and fewer heart failure hospitalizations (0.77, 95% CI 0.70–0.84, p<0.0001) (84).

Strategies for Clinical Practice

Currently angiotensin receptor blockers are used in heart failure patients intolerant to ACE inhibitors or those with side effects deemed untenable. As none of these agents has been shown to improve clinical outcomes in addition to ACE inhibition and β-blockade, no angiotensin receptor blocker should be considered standard therapy in the treatment of heart failure except in the case of ACE inhibitor intolerance.

Aldosterone Antagonists

Activation of the RAAS leads to progression of heart failure through the effects of angiotensin II as well as via aldosterone. The effects of aldosterone are similar to angiotensin II, especially in terms of volume expansion and myocardial fibrosis (85). Its contribution to disease progression was confirmed by the beneficial effects of anti-aldosterone therapy with spironolactone in patients with advanced heart failure (22). In this study, patients with recent class IV symptoms who were still affected by NYHA class III–IV symptoms after optimal therapy were treated with spironolactone or placebo. Spironolactone significantly reduced the risk of death in this population. Eplerenone was recently approved by the FDA for the treatment of hypertension and was proven to reduce the risk of death and major morbidity in patients with left ventricular dysfunction after a myocardial infarction (23).

There are concerns about the use of spironolactone. First, there are no data demonstrating the safety or effectiveness in patients with mild heart failure or in those with ventricular dysfunction after a myocardial infarction. Second, we do not know that this agent is safe when added as a third neurohormonal antagonist to the regimen now considered standard (i.e., an ACE inhibitor and a β-blocker). Although relatively few patients in the Randomized Aldactone Evaluation Study (RALES) were receiving β-blockers, it appears from this post-hoc subgroup analysis that the addition of spironolactone to ACE inhibitor and β-blocker therapy would be a beneficial strategy. Nonetheless, this should not be considered proven. Additionally, patients treated with a β-blocker and an ACE inhibitor could be at increased risk of hyperkalemia if spironolactone were introduced (86). RALES may not have shown a significant incidence of hyperkalemia due to the low use of β-blockers, especially considering the potential effects of β-2 receptor antagonism on potassium homeostasis. Despite the “comfort” physicians have with the use of low-dose spironolactone, a decision to routinely use spironolactone, and to do so more frequently than using a β-blocker would appear imprudent. As a result of multiple studies, β-blockers are now known to be effective irrespective of disease severity, while spironolactone has been studied only in patients with more advanced disease.

Strategies for Clinical Practice

Aldosterone antagonists are undergoing further clinical investigation. Studies will address whether agents that selectively antagonize aldosterone without affecting testosterone are effective, and whether patients with mild disease, those receiving β-blockers, and those with heart failure after a myocardial infarction benefit. In the setting of advanced heart failure, close monitoring of potassium levels is advised even when starting with low doses of spironolactone, and especially with concomitant ACE inhibitor therapy.

Summary

Compelling clinical trial data mandates that all patients with heart failure receive ACE inhibitors and β-blockers. Therefore, the first step to optimize neurohormonal antagonism in heart failure is to employ ACE inhibitors and β-blockers in all patients who could experience benefit. Without doubt, use of these agents should begin at the time of an acute myocardial infarction and should be started in any patient with ventricular dysfunction who is not volume overloaded or unstable. The HOPE study proves that ACE inhibitors should also be administered to those at risk of cardiovascular events (52). Although no study directly addresses this issue, β-blockers also would appear to be rational therapy for patients at risk, considering the pathophysiology of hypertension, coronary disease and heart failure.

In accordance with this view, the recent AHA/ACC guidelines recommend that diabetic, hypertensive, and hypercholesterolemic patients should be treated with medications in stage A that are safe and effective in stages B, C and D as well. This recommendation means that ACE inhibitors and β-blockers should be used as first line therapy, in particular in those with hypertension or coronary disease. While some may argue that this contradicts the recommendations of the most recent recommendations of the Joint National Commission (JNC-7) (87), the two approaches are quite concordant. JNC-7 recommends diuretics along with a second agent and point out that most patients require 2 or 3 drugs to achieve blood pressure of 130/80 or less (87). If the goal is to minimize risk, then the target blood pressure should be 115/75 or less (88, 89) meaning patients will require at least an ACE inhibitor, β-blocker and diuretic.

Consider the typical 50-year-old. Recent studies using intravascular ultrasound suggest that the likelihood of significant coronary atherosclerosis is at least 75% (90). With such a high likelihood of disease based on age or by applying the Framingham risk calculation, such patients are best managed as if they already have coronary disease. In fact, the medications for preventing cardiac events are the same ones that can control blood pressure, ACE inhibitors and β-blockers. Therefore, the optimal neurohormonal antagonism strategy should not stop with widespread use of ACE inhibitors and β-blockers in patients with symptomatic heart failure, but should be extended to include treatment of those patients at risk of developing heart failure. This is the stage A patient, those with hypertension, coronary artery disease, hypercholesterolemia and/or diabetes.

Practical Approach

The most rapid and reliable way to improve symptoms in a congested patient is through the judicious use of diuretics. Importantly, patients who are volume overloaded are not optimal candidates for initiating β-blockers or ACE inhibitors until their volume status has been optimized. When β-blockers are initiated with rapidly increasing doses, the risk of worsening fluid retention is high (50). In contrast, even patients with advanced heart failure tolerate initiation of β-blocker therapy if low starting doses and a gradual up-titration are used, specifically increasing the dose no more frequently than every two weeks (51). In fact, recent data indicates that β-blocker therapy can be initiated at the time of hospitalization, once patients are stabilized, prior to discharge (91). Patients with volume overload and elevated right atrial pressures have a response rate to ACE inhibitors of less than 50% (76), but introduction of these agents in a stabilized patient can be accomplished safely and effectively.

Although ongoing studies appear likely to show an important role for angiotensin receptor blockers, these agents have not been proven beneficial in the studies completed to date, except in patients who are ACE inhibitor intolerant. In contrast, aldosterone antagonism is useful in patients with the advanced disease, but its use requires close monitoring of potassium concentrations for several weeks, especially when used in conjunction with β-blockade and high-dose ACE inhibition.

In clinical practice, the following algorithm should be employed. First, use diuretics to rid the patient of excess volume. This will permit safe and effective introduction of β-blocker and ACE inhibitor therapies. ACE inhibitors can be introduced and increased over the course of 1 – 2 weeks except in the sickest patients, who will require a more gradual schedule. Within the first 2 weeks of initiation, renal function and electrolytes should be monitored (more frequently in sicker patients and in those with serum creatinine concentrations starting above 1.5 mg/dL). Once the optimal dose has been established and renal function is stable, β-blocker therapy should be started. This titration should be more gradual, and patients should be evaluated at each dose increment. Persistent dizziness can be treated with a temporary reduction in ACE inhibitor or diuretic dose, depending on the clinical scenario, and fluid retention responds to increased diuretic dose that generally permits a continued but more gradual up-titration.

Clinical effects of neurohormonal antagonism include improvements in functional status and ventricular function, but even in the absence of such changes, these agents reduce the risk of disease progression and death. These are the ultimate targets of optimal neurohormonal antagonism in patients with heart failure and ventricular dysfunction, and can be achieved by widespread use of β-blockers and ACE inhibitors. Available data mandate use of ACE inhibitor therapy in patients at risk of developing heart failure (52), and the clinical practice of using β-blockers earlier in the development of heart failure appears rational.

Conclusions

Investigators and pharmaceutical companies have focused on the next neurohormonal antagonist, one to complement β-blockers and ACE inhibitors, but have failed. The nature of investigators is to search for the new target and the new therapy, in an effort to change the natural history of disease. Yet the data indicates that the breakthrough treatment for heart failure — and those at risk of developing it — already exists. Neither β-blockers nor ACE inhibitors are prescribed for all eligible patients, and many patients are receiving β-blockers unproven or proven to be inferior, as was demonstrated in COMET (33). Our challenge is to apply the principles of evidence-based medicine, to translate the research findings into clinical practice. Treating patients with stages A, B, C and D heart failure with β-blockers and ACE inhibitors, and where indicated, aldosterone antagonists, is the optimal strategy for neurohormonal antagonism, and by concentrating in particular on the patients with early disease we will have the greatest impact possible on the natural history of the disease.

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Intestinal Metastases from Renal Cell Carcinoma:

A Rare Cause of Intestinal Obstruction and Bleeding

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Abstract

Intestinal metastases from renal cell carcinoma (RCC) are rare. Clinical presentation includes intestinal obstruction, bleeding, or perforation. Management should be aggressive, since the prognosis of RCC is unpredictable and metastasectomy can extend patient survival. We present a patient with intestinal obstruction and bleeding caused by intestinal metastases from renal cell carcinoma and summarize the surgical procedures employed. The relevant literature is briefly reviewed.

Key Words: Small bowel obstruction, gastrointestinal bleeding, renal cell carcinoma, intestinal metastases.

Introduction

Renal cell carcinoma (RCC) is a neoplasm with unpredictable sequelae (1). Although many patients with RCC will develop metastases during the course of their disease, bowel metastases are extremely rare and only a few cases have been reported in the literature (2–11) (Table). We present a patient with intestinal metastases from RCC who was admitted to the hospital with intestinal obstruction and intestinal bleeding. He was successfully treated by intestinal resection. The diagnostic and therapeutic problems are discussed and the relevant medical literature is briefly reviewed.

Case Report

A 65-year-old man was admitted to our hospital complaining of pain in the posterior thoracic wall and left scapula, as well as fatigue and dyspnea. He had a history of RCC in the left kidney and had undergone a left nephrectomy two years previously. The tumor had invaded the renal fascia, and neoplastic emboli were observed within the lymph vessels.

Clinical evaluation revealed tenderness on palpation of the thoracic spine, the left scapula and the right femur. Routine laboratory findings were normal except for a hematocrit of 27%. Bone scan showed increased uptake in the thoracic spine, left scapula and right femur, findings consistent with metastatic disease. During his hospitalization the patient experienced vomiting, abdominal dilatation and melena. Emergency abdominal CT scan showed a marked dilatation of the small intestine and the presence of multiple masses in the lower abdomen adjacent to the loops of the small intestine, which probably caused the intestinal obstruction (Fig. 1). The patient underwent exploratory laparotomy. At surgery, a significant dilatation of the small intestine was observed; some intestinal loops were strangulated in the pelvis. Neoplastic masses were found in the omentum, within the small bowel mesentery and in the intestinal wall, protruding at some places within the intestinal lumen (Fig. 2). The omentum and the terminal part of the ileum (approximately 80 cm) were resected and an end-to-end anastomosis was created. Histology showed metastatic lesions in the omentum and in the wall of the small bowel (Fig. 3). Many of these lesions extended into the adjacent mesentery; two of these metastases were hemorrhagic and protruded within the intestinal lumen (Fig. 2).

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TABLE

Reports of Bowel Metastases of Renal Cell Carcinoma

Author	Ref#	Age (yrs)	Sex	Site of Bleeding	Site of Obstruction	Treatment	T
Hashimoto	11	57	M	Duodenum	—	PPPD	11 years
Ohmura	7	62	M	Duodenum	Duodenum	Embolization-Local resection	5 years
"	"	82	F	Colon (hepatic flexure)	—	Right hemicolectomy	13 years
Deguchi	8	58	M	Terminal ileum	—	Enterectomy	3 years
Heymann	3	40	F	Descending colon	Descending colon	Left hemicolectomy	3 years
"	"	56	F	Cecum	—	Right hemicolectomy	6 months
"	"	64	M	Duodenum	—	Complex procedure@	8 years
Van der Poel	2	54	M	Cecum	—	Iliocecal resection	2.5 years
Robertson	6	70	M	Duodenum (ampulla of Vater)	—	Whipple procedure	13 years
Mascarenhas	12	50	M	Stomach	—	Gastrectomy	4 years

@ gastroenterostomy + vagotomy (first) and ligature of the pancreatoduodenal artery, hemigastrectomy, duodenectomy, choledochojejunostomy, and pancreatic duct ligation
PPPD = pylorus preserving pancreatoduodenectomy; T = duration of the disease to complication
(This table includes patients treated surgically.)

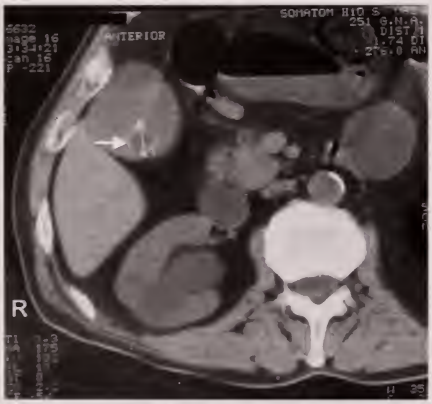

Fig. 1. Abdominal CT scan showing small-bowel dilatation and the presence of masses (arrow) in the intestinal wall.

Postoperative course was uneventful and the patient was discharged on the 12th postoperative day. Unfortunately, he died 9 months later from generalized metastatic disease.

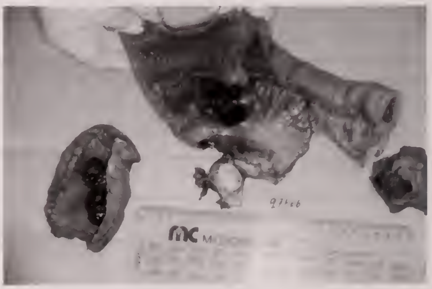

Fig. 2. Operative specimen showing the presence of intraluminal hemorrhagic masses.

Discussion

In approximately one-third of patients with RCC, metastases are present when the primary diagnosis is made (12); moreover, 30–50% of patients with initially localized RCC will develop metastases during the course of their disease (13). Thus, the phenomenon of metastasis will complicate the natural course of RCC in more than 60% of patients (14). However,

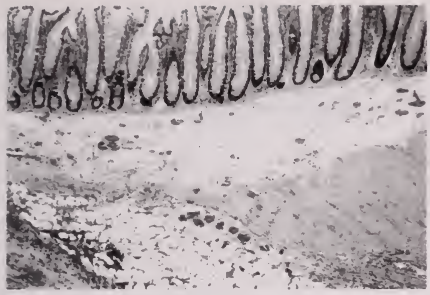

Fig. 3. Histology showed the presence of metastatic cells in the intestinal wall (H & E × 150).

bowel involvement in metastatic disease is uncommon, with only a few reported cases in the international literature (2–12). In a retrospective study of 101 patients with RCC who underwent surgical resection of metastatic lesions (152 procedures), the most common locations of metastases were the lung (n=54), bone (n=42), lymph nodes (n=18), cerebrum (n=12) and other less common sites, such as the spinal canal, thyroid, testis, etc. (2). The bowel was involved in only one patient. Interestingly, ileocecal resection was the third procedure performed on this patient during the course of the disease (2).

The most common clinical presentation of intestinal metastases of RCC is intestinal bleeding (resulting from the invasion of intestinal vessels by the neoplastic disease) (3) and/or intestinal obstruction (as occurred in our patient). Interestingly, it has been reported that gastrointestinal bleeding due to metastatic RCC may be due to metastasis in the pancreas invading the duodenum (4) and metastasis in the ampulla of Vater (5, 6). Intestinal obstruction may be due to the presence of mass(es) within the intestinal wall; however, intussusception of the metastatic lesion as a cause of intestinal obstruction has also been reported (7, 8). Small bowel perforation is a less common presentation of intestinal metastases from RCC (9); it is probably the result of necrosis of the metastatic lesion involving the intestinal wall.

Surgery is justified not only as a palliative procedure, but also because of the unpredictable prognosis for renal carcinoma with secondary disease. Treatment must be individually tailored. The tumor and the involved intestinal section should be removed. Morbidity and mortality for this procedure is at an acceptable level (2). Surgery is indicated not only as a life-saving procedure to manage metastasis-related complications, e.g., intestinal obstruction, gastrointestinal bleeding (as occurred in our patient), but also as an elective procedure which aims to resect the metastatic lesion. Surgery can offer a survival benefit for patients with metastatic RCC (2), and this benefit may not be related to the number of metastases (i.e., solitary vs. non-solitary lesions) (2). Regarding the prognosis, the shorter the interval between the primary tumor resection and the diagnosis of metastases, the shorter the disease-specific survival (2).

In selected cases, intestinal bleeding can be controlled by superselective embolization of mesenteric tumor supply arteries (10). In these cases, the physician should keep in mind that embolization for control of hemorrhage in the small bowel carries a significant risk of bowel infarction.

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Ectopic Intrathoracic Thyroid:

Case Report

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Abstract

We present a patient with ectopic intrathoracic thyroid that was removed through a right lateral thoracotomy. Ectopic intrathoracic thyroid is a rare presentation of thyroid disease and comprises about 1% of all mediastinal tumors. Its removal usually necessitates thoracotomy or sternotomy. The relevant literature is briefly reviewed.

Key Words: Goiter, thyroidectomy, retrosternal goiter, ectopic intrathoracic goiter.

Introduction

Ectopic intrathoracic thyroid is a very rare presentation of thyroid disease, comprising 1 – 3% of retrosternal goiters and about 1% of mediastinal tumors (1). Thoracotomy or sternotomy is usually required for resection of the ectopic thyroid tissue. We present a case of ectopic intrathoracic thyroid in a patient with multinodular goiter. The relevant literature is briefly reviewed.

Case Report

A 40-year-old patient presented to our department for surgical management of a multinodular goiter. Preoperative evaluation, which included chest radiography, scintigraphy (I^{131}), and chest computed tomography, revealed intrathoracic ectopic thyroid tissue at the right side of the posterior mediastinum, behind the great vessels, extending to the level of the bifurcation of the trachea (Figs. 1 – 3). The intrathoracic thyroid tissue could not be removed through the cervical incision, and a right lateral thoracotomy was performed (Fig. 4). The intrathoracic thyroid was not connected to the cervical thyroid. Blood was supplied from intrathoracic vessels, thereby establishing the diagnosis of an ectopic intrathoracic thyroid. The ectopic thyroid was easily removed through the thoracotomy. The postoperative course was uneventful. Histology showed colloid multinodular goiter in both the cervical and ectopic thyroids.

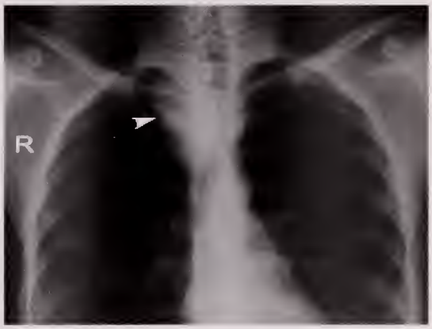

Fig. 1. Chest X-ray showing a mass (arrow) in the superior mediastinum with deviation of the trachea.

Discussion

Retrosternal goiter is the result of progressive enlargement of the thyroid parenchyma, which

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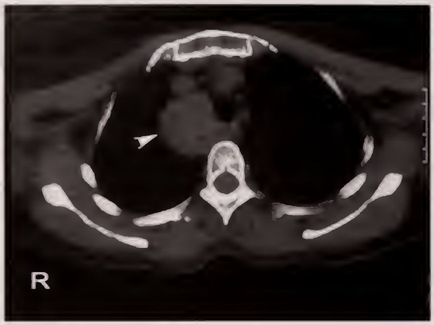

Fig. 2. Chest computed tomography. Ectopic thyroid tissue (arrow), behind the great vessels, at the right side of the posterior mediastinum.

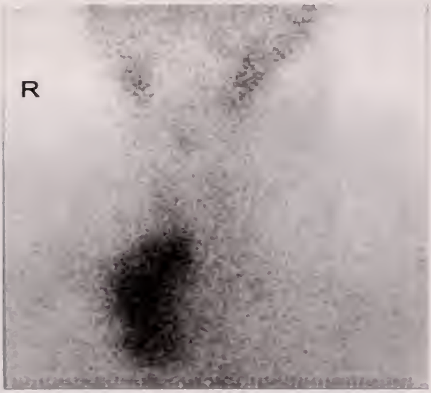

Fig. 3. Scintigraphy (I^{131}) showing the presence of intrathoracic thyroid tissue.

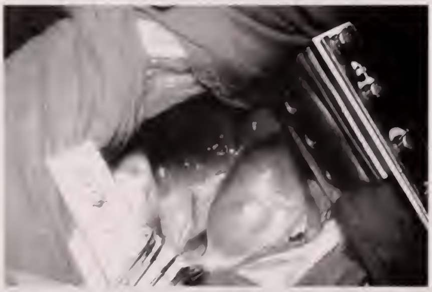

Fig. 4. Operative findings; the ectopic intrathoracic thyroid.

extends behind the upper part of the sternum within the superior mediastinum (anterior part). Also called "secondary intrathoracic goiter," it is not uncommon in patients with thyroid disease (1–6%) (2). Blood supply of secondary intrathoracic (or retrosternal) goiter is from the superior and inferior thyroid arteries. The presence of ectopic intrathoracic thyroid tissue in the mediastinum is a very rare entity, called "primary intrathoracic goiter" (3, 4). What distinguishes ectopic intrathoracic thyroid from the much more common retrosternal goiter is that the former receives its blood supply from vessels of the mediastinum (rather than the neck) and it is not otherwise connected to the cervical thyroid except for a thin band of connective tissue. When present, symptoms in patients with primary intrathoracic goiter (ectopic intrathoracic thyroid) are due to the presence of the mass (pressure on adjacent tissues/organs) (Table 1) (1, 3, 4). Differential diagnosis includes a variety of diseases (Table 2) (5). Chest radiography is usually diagnostic for most patients (up to 90%) (6). Chest computed tomography provides important information, with high sensitivity (98%), about the location of the ectopic thyroid tissue and its relation with the great vessels and other structures in the mediastinum (4, 6, 7). Since uptake of the I^{131} is not always observed in ectopic intrathoracic thyroid tissue, scintigraphy (using I^{131}) is not always diagnostic (7). However, it may be useful when

TABLE 1

*Symptoms of Patients with Ectopic Intrathoracic Thyroid (Primary Intrathoracic Goiter)**

- Respiratory symptoms (cough, wheezing, dyspnea, hemoptysis, recurrent pneumonias, etc.) (the most common symptoms)
- Dysphagia (rare)
- Weight loss (in malignant lesions) (rare)
- Superior vena cava obstruction (in very large lesions)
- Chest pain (very rare)

* About one-third of patients are asymptomatic.

TABLE 2

Differential Diagnosis of Mass Lesions in the Posterior Mediastinum

- Lymph node lesions
- Bronchogenic cysts
- Aneurysms
- Neurogenic tumors
- Pheochromocytoma
- Ectopic thyroid
- Spinal lesions
- Hiatal hernia

positive. Ectopic intrathoracic thyroid should be removed to rule out malignancy (1, 3, 6). Excision of this tissue is usually not possible through the cervical incision, and so a thoracotomy or sternotomy is required. This is a safe procedure with a very low mortality rate (0–2%) (1, 3, 4) and an acceptable morbidity. Prognosis is excellent following a successful excision (7).

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If I Were Dean:

A Challenge to New Medical Students

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Abstract

If I were Dean I would welcome new students by explaining that they will be trained to become humane, compassionate scientists, and that our medical sciences are based on classical Greek science and medicine, with its first aphorism “Life is short, but art and skill are long.” Science involves the conception and construction of refutable hypotheses, and their testing by repeatable experiments, followed by publication of the results. Thus, science is uncertain, tentative, probabilistic and universal. Our students will learn compassion both from our bioethicists and from faculty role models. I would warn the students that, unfortunately, much of the general public has little understanding of science, does not accept our medical model, and is increasingly seeking alternative, pre-scientific, non-scientific and even pseudo-scientific models of care, not necessarily from lack of intelligence, but perhaps more from scientific illiteracy and innumeracy. And the public fruitlessly demands safe and effective drugs, free from side effects, for all ailments, but they often fail to take drugs when prescribed, and/or take alternative medicines instead.

Key Words: Medical students, science, pseudo-science, compassion.

Welcome to our school of medicine. After three and a half years you will all, or almost all, become physicians qualified for lifelong careers (which includes lifelong learning).

You have been chosen carefully, from thousands of applicants, for your intellect, conscientiousness, pertinacity, poise, self-confidence, work experience, and extracurricular interests and achievements. Deans often proclaim the ambitions of their curricula. Instead, for my subject, I have chosen a simple definition: A physician is a humane, compassionate scientist. I shall start with science, and its definition.

You may be surprised to learn that the medical sciences we shall teach you are, in origin, Greek science and Greek medicine. In the ancient world, medicine was based on the belief that diseases were sent by the gods, from whom relief should be sought. But about two and a half thousand years ago, the Greeks began to believe that diseases were not divine in origin, so that their causes must be sought in the natural world. And they began to believe that physicians should be taught to reason and experiment, and perhaps above all that sequence was not proof of consequence. Dissection of animals and humans laid the foundation for anatomy, and experimentation led to physiology. Greek medicine spread both west to the Roman Empire and east to India and beyond. After the fall of Rome, the loss of Greek texts was fortunately alleviated by translations into Arabic, Hebrew and Latin by Muslim, Jewish and Christian scholars, who together helped lay the groundwork for Renaissance medicine and science – and ultimately, modern medicine.

Here is the oldest and most famous aphorism of medicine and medical education (1): ‘Ο βιος βραχυς, ‘η δε τεχνη μακρη: (*Ho bios brachys, hē de technē makrē*): “Life is short, art is long.” The saying has implications for you as medical students. You will begin studies here that, hopefully, you will continue far into the future. At the same time, we may need to re-

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strain the enthusiasm of your instructors to teach you "everything" in their fields – for that would be unrealistic and impossible in four years.

Without doubt these next four years will be as difficult and demanding as they were in Glasgow in 1786 (2): "While we admit that experience and observation are the surest guides in the practice of medicine, it must be granted at the same time, that to make judicious experiments from what we observe, not to confound the effects of one cause with those of another, and to apply our experience and observations to the best purpose, is not easy, nor so common a thing as is usually believed."

What Is Science?

As a young man, I understood science to be the acquisition of knowledge of the universe by experiment, and also accepted Kelvin's definition, "Science is measurement," i.e. biometry and statistics. I don't recall being taught then that scientific theories or laws were based on the testing of hypotheses. I was not aware until the 1980s that conceptual precision and observational testability might also require *falsifiability* (3), and only recently did I learn that predictive *verification* may be just as important as *falsification* in the production of scientific knowledge (4).

I would now say that science is "the conception and construction of refutable hypotheses, their testing by repeatable experiments, followed by publication of the results." The corollary is that scientific hypotheses can never be totally proved or disproved. "Theories are not verifiable but they can be corroborated.... Every scientific statement must remain *tentative forever*" (3). "Science proceeds when earlier hypotheses are refuted by data, and awareness of this history of 'conjecture and refutation' is what stimulates new hypotheses" (5). Charles Darwin put it even more simply in 1861: "How odd it is that anyone should not see that all observation must be for or against some view if it is to be any service" (6). "Science is truth-seeking, it is uncertain and is subject to constant revision.... Causation in science is probabilistic and universal" (7).

I tried to plan research, both my own and that which I supervised, by such a scheme. However, I found that my graduate students did not recall being taught anything about the nature of science. I therefore performed pilot studies both in England and in the U.S. I asked those questioned to write, anonymously, in one sentence, what they understood by the term "science." Almost every answer expressed acquisition of knowledge of the universe, so that when scoring, I searched for the terms "hypothesis," "theory" and "experiment." (No one mentioned either "corroboration" or "falsification.") Of 25 final year medical students in London, only five used "experiment," only one "theory" and none "hypothesis" (8). Of 18 undergraduate science students in the U.S. only three used any of these terms. Of schoolgirls, ages 16 – 18, at an independent English school, none of the 11 studying sciences mentioned any of these terms; two of the seven studying liberal arts mentioned "experiment," but none used "hypothesis" or "theory." Two thousand upper secondary students in the U.K. in 1992 confused science with technology, and 46% held that science could rest on the assumption of an intervening deity (9).

Humanity and Compassion

I assume that you will learn genuine science here. My next question is whether humanity and compassion can be taught. Virtue-based ethics applied to medicine seeks to produce a physician with such virtues as benevolence, compassion, courage, fidelity, honesty and truthfulness (10). How these aims are best achieved, by teaching or by practice, has been discussed ever since Socrates. Actually, both are important. Here, the theory will be taught well by our bioethicists. You will observe the practice of our faculty, and I trust that you will find some of them helpful role models for your own future practice, and for your own skills, which you will pass on to future medical students.

You will forgive me, I hope, if I raise the issue of behavior in the hospital, especially with patients. Medical students are young and full of life, and for centuries it has been a challenge to rein in their boisterousness. In 1778, the municipal government of Edinburgh required that its medical students display "a composed and decent carriage [i.e. social behavior]," because levity, "almost the inseparable characteristic of youth in any profession [would prevent the students] from paying compassionate attention to the patients.... The majority of young gentlemen who walk our different hospitals are little under the dominion of the humane power of sympathy.... Thus [physicians and teachers should] recommend by precept and enforce by example the humane attention here recommended [because] humanity will always stamp a dignity on the profession" (11). Here at Mount Sinai, New York's first neurologist "stressed the importance of the doctor looking neat, being scrupulously clean, using good English, and articulating distinctly" (12). Clear communication is always a valuable tool for the physician.

The Medical Model and the Public

I have now explained how you can become a humane, compassionate scientist and a skilled physician, and you may feel that all I need do is wish you well. Not so.

Given the widespread lack of scientific understanding, you will not be shocked to learn that much or even most of the public does not accept our medical model and seeks alternative, pre-scientific, non-scientific and pseudo-scientific models of care (13). Between 1990 and 1997 the number of Americans using complementary and alternative medicine (CAM) rose from 25% to 42%, with an increase of 50% in expenditure on alternative therapies. In primary care there were 386 million visits to physicians and 629 million visits to CAM practitioners (14). The use of herbal remedies increased fourfold, so that half of all adult Americans now take dietary supplements, and in 2001 they spent $4.2 billion on herbs and other botanical remedies (15). Greek physicians faced the same problem 2500 years ago, and in Saxony in 1900 there were 2,029 legally qualified physicians and 1,578 known illegal practitioners (16).

Why do so many people seem to prefer alternatives to science? Is it a question of intelligence? There may be an "intelligence gap" of sorts between physicians and the general public. However, those seeking alternative medicine or science are drawn from the least to the most intelligent in the land. The wife of one recent President consulted an astrologer to plan the timing of her husband's trips; another held imaginary conversations with a dead predecessor, Eleanor Roosevelt. It is reported that the wife of a certain prime minister had toxins scrubbed out of her body in a shower, wore inflatable trousers to combat leg bloat, and had "stress-fighting" acupuncture earrings and a bioelectrical shield to ward off radiation from personal computers. She also consulted, in person or by fax, a psychic on spiritual questions and had a "rebirthing ceremony" with her husband, in which they shouted and smeared mud and fruit pulp on each other (17).

If lack of intelligence is not the problem, then do patients simply not trust physicians? No. Surveys show that doctors are among the most trusted sources of advice, followed by teachers, whereas our principal critics – journalists and politicians – are considered the least trustworthy.

As I suggested earlier, the problem may be one of scientific illiteracy and innumeracy. Of 1,574 adult Americans surveyed recently, 66% were quite interested in new discoveries in medicine and 50% in science, but only 57% had some idea of probability, only 43% were familiar with the nature of experiments, and only one-third could explain what it means to study something scientifically (13). Only 22% could define a molecule, 48% believed that the earliest humans lived at the same time as the dinosaurs, and 49% thought that antibiotics kill viruses.

What causes this lack of scientific knowledge? Americans learn about science mostly from TV (44%), compared to newspapers (16%), magazines (16%), the internet (9%), radio (3%), friends (3%) and books (2%). In 1999, only 41% of Americans read a newspaper (1990: 57%), but 63% watched one or more hours of news each day on TV. Adults spend more than 1000 hours a year watching TV, of which they spend 408 hours watching news, which includes 81 hours of science news. That might be informative, but we do not know how closely TV news is watched, because many American families watch TV at the same time that they eat dinner (18).

Whatever the cause, pseudo-science reigns. Two-thirds of Britons read their horoscope daily, and one-fifth believe in its predictions for them. In the U.S., 41% believe astrology is at least somewhat scientific, and 60% claim that some people possess psychic powers or extrasensory perception (ESP). Half the American population believe God made humans in the last 10,000 years. Two-thirds of Americans believe creatures somewhere else in the universe have recently been in touch with humans, and half of this majority believe that aliens have abducted humans. Some 80% of Americans believe that their government knows more about unidentified flying objects (UFO's) than it admits.

Another possible reason for the popularity of alternative medicine is that medical practitioners may not communicate effectively with their patients. How could you remedy this defect? First you should look at your patient's stance and gait, and above all at the face to learn to recognize anger, disgust, embarrassment, fear, sadness, surprise and pain (19). Knowing your patient's mood is a vital first step in communicating what he or she is willing and able to hear. You should then open your ears and keep your mouth closed for at least two minutes, an amount of time that was sufficient for nearly 80% of Swiss patients to express all their volunteered symptoms. In America a patient is given an average of only 22 seconds of uninterrupted time by the doctor (20). Thus, alternative practitioners are sought because they give patients the satisfaction of being listened to for a half or a whole hour. Such practitioners soon recognize when there is no organic disease, and can then safely predict that trivial, self-limited ailments will resolve rapidly, coinciding with the taking of harmless remedies.

"Drug Problems"

The public demand medications to cure all ailments, and each drug must be completely effective and completely safe. There is little understanding that their demands are impossible because all drugs are only partially effective and only relatively safe. I was once asked to go to Washington to recommend the approval of a drug that was already licensed in Europe. The firm wanted to know how I would reply to the question, "Does this drug have side-effects?" I said I would reply, "Certainly! I would never use a drug without side-effects, because it would be therapeutically inert." The firm decided not to let me testify on their behalf.

A related problem that patients have with medications is an unwillingness to take them. One major triumph of clinical medicine is the treatment of high blood pressure with daily tablets to prevent heart disease and strokes. Yet half the patients with hypertension do not take these tablets when they have been prescribed (21). And, conversely, half the patients who do take maintenance treatment for their illness also take alternative medicines, but do not tell their physicians about them (22). Thus, many patients seem to believe that physicians prescribe drugs too readily, that drugs are best avoided as unnatural and unsafe, and above all that taking drugs for the rest of one's life means that one is ill. Being labeled "ill" is the dreaded fear of all patients, because it reminds them daily that "life is short," upsetting news that patients and even physicians like to suppress, in particular the unmentionable fact that all our patients die eventually.

You may believe that noncompliance with therapeutic advice would not be a problem for university students. Yet it is. Although physicians discourage, and would like to ban, tanning lamps because they are carcinogenic, they are used by 25 million Americans, especially young adults. A 1999 survey at a large U.S. university found that 47% of the students, especially the women, were currently using such lamps, and an additional 15% had in the past. Yet 90% of users were aware that skin cancer and premature aging were possible complications (23).

Similarly, sunbathing for a "healthy tan" is common in Cornwall, England, in spite of the fact that more than 90% of the sunbathers (24) and 94% of Britons generally (25) know the risk of skin damage and cancer. How could you persuade your patients to do what is clearly in their own self-interest when they don't wish to? Oxford epidemiologists suggested a novel approach to discourage British teens from smoking: Tell them that for every thousand young people who smoke cigarettes, one would be murdered, six would be killed in traffic accidents, and 250 would die prematurely from smoking (26).

Mount Sinai's Situation

Your curriculum here will be similar to that of other medical schools. But you should find it especially stimulating here, because this center is not only set in the greatest city in the world, but also adjoins two neighborhoods noted for sharply contrasting levels of income and prosperity. Here and in our associated hospitals, you will meet a variety of cultures, languages and religions, and people in nearly every type of profession. This variety is perhaps New York's greatest strength. You will also be faced with human dysfunction, not only among the poor, who may lack decent education, health care and homes, but also among the ultra-rich, who may worry about whether a million dollar donation might help their child's admission to a favored nursery school, then a private school, and eventually an ivy league college (27). Both rich and poor include some who suffer from alcohol or drug abuse, or sexually transmitted diseases, or physical or emotional abuse of children or spouses.

Our library is first class, and you are only two blocks away from the New York Academy of Medicine with an excellent medical library of its own. But you must not study all the time.

New medical students at Oxford in 1933 were advised to "keep an hour or two now and then for the cultivation of at least one hobby...completely divorced from your professional studies...to preserve your mental elasticity and to provide you with a handy and welcome respite from the strain of your life's work" (28). Across Fifth Avenue you have one of the finest urban parks in the world. The 92nd Street Y has a wide range of distractions. There is a public lending library on 96th Street, and the superb research library at 42nd Street. Within a few blocks are the Jewish Museum and the Museum of the City of New York, both free with your ID. Nearby is the Guggenheim and the great Metropolitan Museum. Our Recreation Office offers free or inexpensive tickets for opera, ballet, musicals, plays and baseball games. All of these are for you.

Postscript

When a former chief of medicine gave our 2002 commencement address, he admitted that he could not "remember a single word of the commencement address when [he] graduated from medical school, or even who gave the address" (29). In wishing you well in your time here and your future careers, I do not expect you to remember my name either. But perhaps you will remember that you are heirs to an ancient tradition of science tempered with compassion and humanity. My best wishes to you.

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Recombinant Interferon Gamma-lb and Low-Dose Steroid in Two Pediatric Cases of Nonspecific Interstitial Pneumonia

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Abstract

We report two young girls, the first almost 18 years old and the second 12½ years old, affected with nonspecific interstitial pneumonia, both diagnosed at the age of 11 by open lung biopsy and both being treated with low-dose steroid. Due to insufficient response to conventional therapy and based on positive therapeutic results following the use of subcutaneous recombinant interferon gamma-1b in fibrosing interstitial pneumonias of adults, they were given a 1-year trial of subcutaneous recombinant interferon gamma-lb in association with a steroid. Our experience with these two young patients suggests that interferon gamma-lb cannot be considered as stabilizing or a curative therapy to control or reverse nonspecific interstitial pneumonia unresponsive to steroids alone.

Key Words: Interferon gamma, steroid, nonspecific interstitial pneumonia, pediatrics.

Glossary

ERV:	expiratory residual volume
FEV_1:	forced expiratory volume in 1 second
FVC:	forced vital capacity
IFN:	interferon
NSIP:	nonspecific interstitial pneumonia
$paCO_2$:	arterial carbon dioxide tension
paO_2:	arterial oxygen tension
SVC:	slow vital capacity
Th 1:	T-helper type 1
Th 2:	T-helper type 2

Introduction

Nonspecific interstitial pneumonia (NSIP) is a chronic disorder of the lung characterized by inflammatory cell infiltration of the interstitium and fibrosis within the alveolar walls; these changes appear to be temporally and firmly uniform in most cases (1). The biologic scenario of fibrosing interstitial diseases is characterized by the shift of T lymphocytes in favor of the T-helper type 2 (Th 2) reaction, which is followed by reduced production of interferon (IFN) gamma, a main mediator of the T-helper type 1 (Th 1) reaction (2–4). The antifibrotic properties of IFN gamma have been demonstrated to inhibit collagen synthesis *in vitro* and *in vivo* (5, 6). We have evaluated the possible beneficial effect of recombinant IFN gamma-1b for a 12-month period in two young girls with NSIP, who had received a constant low-dose steroid. Subcutaneous recombinant IFN gamma-1b (provided by Boehringer Ingelheim, Italy) was added to their regimen three times a week and oral low-dose prednisone was continued. IFN gamma-lb was used at an initial dosage of 100 μg and maintained until the third month, when it was increased to 150 μg and finally increased to 200 μg at the fifth month of treatment. Prednisone was used at a dose of 15 mg on alternate days. Methods and results of our investigation are reported.

Patients and Methods

Patient 1, female, born full-term after normal pregnancy and delivery to a first gravid, complained of occasional dry cough and dyspnea with medium exertion (with otherwise normal vital signs), at the age of 11 years. Routine laboratory findings were unrevealing. Chest X-ray showed a diffuse thickening of the alveolar walls. Chest high-resolution computed tomography showed a predominantly subpleural distribution of reticular opacities with septal thickening. Spirometry revealed severely reduced slow vital capacity (SVC), 420 mL (18.1% predicted) (7). Blood gas analysis showed profound hypoxemia, with the paO_2 of 72 mm Hg (normal range 75 – 100) with maximal exertion. The paO_2 was normal at rest. Open lung biopsy

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showed NSIP (Fig. 1). She was started on prednisone (60 mg/m^2/day). Pulmonary function remained unchanged. Prednisone was reduced to 15 mg on alternate days without interruption. Her condition appeared to be stable for five years. Thereafter, blood gas revealed a paO_2 of 68.3 mm Hg and $paCO_2$ of 45.4 mm Hg, normal range 35–45, breathing room air. A reduction of lung volumes occurred. Transbronchial biopsy and bronchoalveolar lavage were refused by the patient's relatives. After we had obtained an informed consent, when the patient was 17 years and 10 months, IFN gamma-lb therapy three times/week was proposed, combined with maintenance prednisone dose (15 mg on alternate days) for 1 year.

Patient 2, female, born full-term after uncomplicated pregnancy and delivery to a third gravid, complained that she was unable to climb one flight of stairs or walk to school. She noted cyanosis with exercise and digital clubbing at the age of 11 years. Typical respiratory symptoms, such as shortness of breath, emerged about 10 months after the first clinical evaluation. Chest radiograph revealed peripheral reticular opacities without cardiomegaly or hilar adenopathy (Fig. 2), and chest high-resolution computed tomography revealed a diffuse thickening of the interstitium. Echocardiography failed to show pulmonary hypertension. Spirometry revealed reduced SVC, 1240 mL (62.9% predicted) (7). Blood gas analysis showed paO_2 of 74 mm Hg, on maximal exertion, which reversed to normal with rest. Neither bronchoalveolar lavage nor gallium lung scintiscan confirmed an active inflammation. Open lung biopsy revealed NSIP. Treatment included prednisone (60 mg/m^2/day), slowly reduced to 25 mg on alternate days. She remained stable for about 1 year. At age 12 years and 6 months, IFN gamma-lb therapy three times/week combined with a maintenance dose of prednisone (15 mg on alternate days) was instituted and maintained for 1 year.

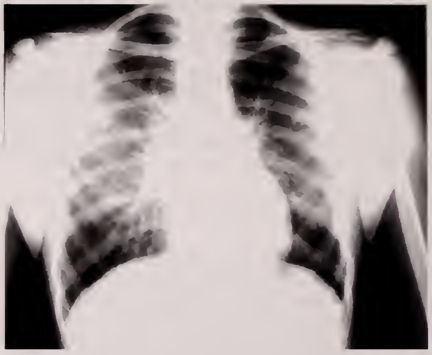

Fig. 2. Chest AP X-ray from patient 2, revealing bilateral reticular infiltrates most prominent in the lower lobes, indicating chronic interstitial pneumonia.

The table summarizes our assessment of SVC, expiratory residual volume (ERV), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), all expressed in mL, arterial oxygen/carbon dioxide tension (paO_2/$paCO_2$) at rest, expressed in mm Hg, and a six-minute walk test under conditions of standardized ergometry (with the distance covered dur-

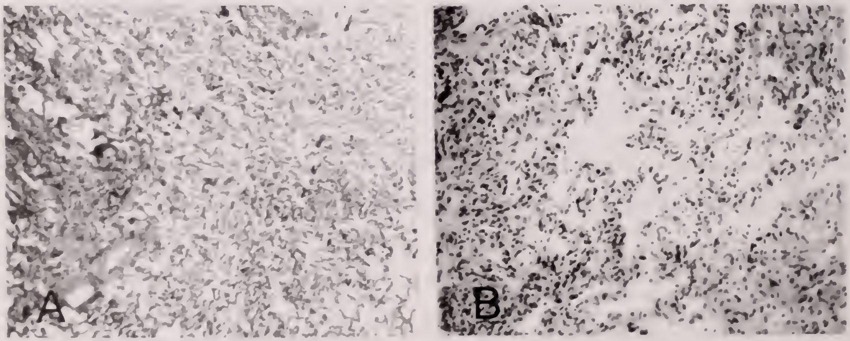

Fig. 1. Percutaneous open lung biopsy from patient 1. In panel **A**, a low-power magnification, edema and fibrosis within alveolar septa and interstitial inflammatory infiltrates are apparent. In panel **B**, a high-power magnification, hyperplasia of type 2 pneumocytes and chronic inflammation prevalently characterized by lymphocytes can be recognized.

TABLE

Functional Measurements for the Two Patients

	pre IFN g-1b	1 month	3 months	6 months	9 months	12 months
Patient 1						
SVC (mL) (% predicted)	760 (22)	980 (28)	740 (21)	780 (22)	640 (19)	560 (17)
ERV (mL) (% predicted)	480 (34)	580 (40)	480 (34)	450 (32)	130 (9)	160 (11)
FVC (mL) (% predicted)	1030 (28)	720 (20)	700 (19)	730 (20)	500 (15)	540 (16)
FEV1 (mL) (% predicted)	430 (13)	450 (14)	450 (14)	430 (13)	310 (10)	340 (11)
paO_2 (mm Hg) at rest	68.3	68.7	76.7	69.9	63.8	75.8
$paCO_2$ (mm Hg) at rest	45.4	45.6	44.0	47.4	48.0	45.5
O_2 saturation at rest (%)	94.0	93.9	94.9	93.6	92.5	95.2
Distance covered (m)	250	300	300	230	330	300
O_2 sat. (%) after walking test	70–75	75–80	80–84	81	75–80	75
Patient 2						
SVC (mL) (% predicted)	1470 (67)	1510 (69)	1370 (57)	1390 (61)	1400 (62)	1150 (48)
ERV (mL) (% predicted)	410 (69)	490 (82)	410 (69)	480 (80)	540 (90)	500 (84)
FVC (mL) (% predicted)	1550 (64)	1560 (64)	1370 (57)	1360 (60)	1400 (62)	1150 (48)
FEV1 (mL) (% predicted)	1410 (72)	1390 (71)	1220 (54)	1210 (57)	1250 (58)	1270 (59)
paO_2 (mm Hg) at rest	93.7	94	94.5	104.9	91.6	95.8
$paCO_2$ (mm Hg) at rest	33.8	34.5	32	28.3	32.5	33.1
O_2 saturation at rest (%)	95	95	94	97.9	96.9	97.4
Distance covered (m)	600	550	550	450	450	450
O_2 sat. (%) after walking test	88	86	87	82	90	90

ing the six minutes expressed in meters and oxygen saturation during the same time expressed in %) (8). Examinations took place prior to the beginning of treatment, after one month, and then every three months during the year of observation. Improvement of pulmonary function was defined as a 10% increase in predicted value of SVC, ERV, FVC and FEV_1 or a 3% increase in oxygen saturation with the same fraction of inspired oxygen, resting or after exertion.

Discussion

The efficacy of any treatment for chronic interstitial pneumonias has been shown to be related to strict histological criteria (9). NSIP generally displays a relatively quiescent fibrosis, but sometimes the mixture of persistent inflammation and active fibroblast proliferation appears to worsen, so that NSIP might resemble the clinical features of usual interstitial pneumonia (10). There are good theoretical reasons why IFN gamma-lb might be beneficial in fibrosing interstitial pneumonias. Moreover, supporting evidence comes from studies demonstrating that interferons, especially IFN gamma, a major Th1 cytokine, have profound suppressive effects on the synthesis of extracellular matrix, inhibiting both fibroblast and chondrocyte collagen production *in vitro* as well as decreasing procollagen gene transcription *in vivo* (11–13). When fibrosis is not completely established, further progression could be prevented by IFN gamma therapy, helping the shift of cytokine expression toward a more normal Th1/Th2 balance (14). The first positive results are attributed to Ziesche et al., who treated 9 adult patients with idiopathic pulmonary fibrosis, with IFN gamma-1b and prednisolone. Significant benefits were observed in the physiological parameters (15). The decision to treat our two young patients with subcutaneously injected IFN gamma-lb plus oral steroid was based on these results, and our assumption that NSIP belongs to the group of fibrosing pneumopathies and that its natural history may in some way become more aggressive with a tendency to massive lung fibrosis.

Both patients completed the study. The main side effects from IFN gamma-1b administration were fever in the first month of treatment in both patients and sporadic dizziness in patient 1. During the last months of the trial an increasing muscular weakness with fever emerged in both. Acetaminophen was prescribed.

No improvement was noted in our patients. We recorded only a partial response of SVC in the first month of treatment, while FVC and FEV_1 in both patients decreased. Blood gases at rest, distances covered during the walk test, and oxygen saturation remained unchanged for both patients during the observation period. Nor did high-resolution computed tomography performed at the beginning and at the end of the study show any improvement. On the contrary, it revealed patches of "ground-glass" areas alternating with normal areas of the lung in patient 1 (Fig. 3). Right ventricular ejection fraction measured by echocardiography prior to the study, at six months, and at the end of treatment remained unchanged.

There are several possible explanations for our patients' lack of response to treatment. The effectiveness of IFN gamma-lb has been demonstrated in only a single preliminary study related to idiopathic pulmonary fibrosis. The range of IFN gamma bioactivity is rather wide and its action may prove to be nonspecific. Only 2 pediatric patients were studied. Any effect of IFN gamma might depend on the extent of fibrosis in NSIP. And finally, initial lung functional tests may be insufficient to predict the extent of response to treatment. Nonetheless, it is possible that progression of the disease may have been retarded by IFN gamma, but longer clinical follow-ups and histologic evidence would be required to make such a judgment. However, from this experience with two pediatric patients, IFN gamma cannot be considered effective treatment for patients with NSIP. The exact role of IFN gamma-1b in the treatment of pediatric NSIP or other fibrosing interstitial pneumonias needs to be determined by large, multicenter, clinical efficacy trials.

Acknowledgments

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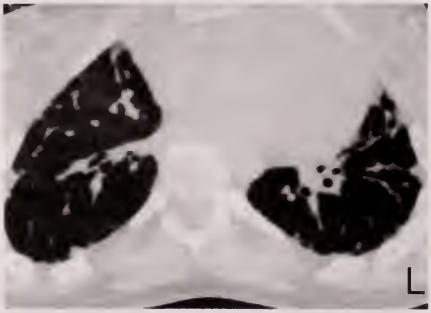

Fig. 3. A representative high-resolution CT scan of the thorax from patient 1 after the conclusion of the trial, showing patches of intralobular linear opacities and irregularly thickened septa which alternate with normal-appearing areas.

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OLUME 71 NUMBER 3 MAY 2004

ADOLESCENT MEDICINE

Angela Diaz, guest editor

Introduction: The Mount Sinai Adolescent Health Center *Angela Diaz* 146

Fostering Resilience in Adolescent Females *Lorena M. Siqueira and Angela Diaz* 148

Nutrition and Eating Disorders in Adolescents *Marjorie E. Kaplan Seidenfeld, Elyse Sosin, and Vaughn I. Rickert* 155

Adolescents and Immunization: Tips for the Primary Care Provider *Sharon Edwards and Angela Diaz* 162

Foster Children with Special Needs: The Children's Aid Society Experience *Angela Diaz, Sharon Edwards, Wendy P. Neal, Paula Elbirt, Mandy Rappaport, Rudd Kierstead, and Beverly Colon* 166

Obtaining a History of Sexual Victimization from Adolescent Females Seeking Routine Health Care *Angela Diaz, Sharon Edwards, Wendy P. Neal, Pamela Ludmer, Stephen B. Sondike, Carol Kessler, Daniel Medeiros, and Anne T. Nucci* 170

Where The Wild Things Are: The Power and Challenge of Adolescent Group Work *Seth Aronson* 174

Legal and Ethical Issues Facing Adolescent Health Care Professionals *Angela Diaz, Wendy P. Neal, Anne T. Nucci, Pamela Ludmer, Jacalyn Bitterman, and Sharon Edwards* 181

CHIP: New Opportunities in Adolescent Health Care Delivery *Angela Diaz, Sharon Edwards, Wendy P. Neal, Pamela Ludmer, Jacalyn Bitterman, and Anne T. Nucci* 186

Adolescent School-Based Health Care: A Description of Two Sites in Their 20th Year of Service *Doris R. Pastore and Beth Techow* 191

continued inside

SAINT BARNABAS HEALTH CARE SYSTEM

LIBERTY HEALTHCARE SYSTEM, INC.

Veterans Affairs

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Volume 71
Number 3
May 2004

CONTENTS *continued*

GRAND ROUNDS

Update in Atherothrombotic Disease *Juan F. Viles-Gonzalez, Sunil X. Anand, Carolina Valdiviezo, M. Urooj Zafar, Randolf Hutter, Javier Sanz, Teresa Rius, Michael Poon, Valentin Fuster, and Juan J. Badimon* 197

ABSTRACTS

Research in Medicine 2003—Jersey City Center 209

Research in Medicine 2003—Queens Hospital Center 211

Information for Authors i

Introduction:

The Mount Sinai Adolescent Health Center

Angela Diaz, M.D.

THIS SPECIAL ISSUE on adolescent health care commemorates the 35th anniversary of the Mount Sinai Adolescent Health Center (AHC). Dr. Joan Morgenthau founded the Center within the Department of Pediatrics in 1968. AHC has had three directors: Dr. Morgenthau (1968–1972); Dr. Les Jaffe (1972–1989); and Dr. Angela Diaz, since 1989.

Over the past 35 years, the AHC has earned a national reputation as being one of the largest and most comprehensive health care centers in the country dedicated exclusively to youths aged 10–21 and their children. AHC's mission has been to provide comprehensive, adolescent-friendly, culturally sensitive and age-appropriate health services to adolescents in New York City and beyond. Services are provided regardless of ability to pay, confidentially is maintained, and there are no geographic restrictions.

AHC Services

AHC uses a culture-centered interdisciplinary approach to the physical, reproductive, and mental health of adolescents, in addition to providing education and related services. Most important, AHC staff strives to build the skills of the young people it serves so they can become responsible health care consumers. AHC's comprehensive medical services include primary and specialty care, acute care, health education and risk reduction support. Reproductive health services include pelvic examinations, pap smears, pregnancy testing, pregnancy options counseling, family planning services and colposcopy, as well as screening and testing for sexually transmitted infections and HIV. AHC's mental health services include psychotherapy, psychoeducation and crisis intervention for individuals, families, and groups. Group programs assist survivors of sexual abuse, incest and rape; HIV-infected and -affected youth; substance abusers; young women with same sex partners; depressed girls; and more.

Community-Based Programs

In 1982, AHC established New York's first high-school-based health center at the Manhattan Center for Science and Math High School, and in 1983 AHC began a second high-school-based health center at the Julia Richman Education Complex. Both centers see thousands of adolescents every year for medical and mental health services and health education.

In 1988, AHC began the Sinai Peers Encouraging Empowerment through Knowledge (SPEEK) peer-education program, which employs the AHC's patients and local adolescents as peer educators in HIV/AIDS prevention education. SPEEK peer educators participate in a 60-hour training curriculum and then offer a wide variety of HIV/AIDS prevention, advocacy, and peer-to-peer activities at AHC, community agencies and schools, and at various local and citywide forums. Under the supervision of peer-education supervisors and a health educator, SPEEK peer educators conduct workshops in schools and communities, and develop health education materials for patients at the AHC.

Training Programs

AHC educates health care professionals from all over the United States and other coun-

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From the Division of Adolescent Medicine, Department of Pediatrics, The Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Angela Diaz, M.D., Director, Mount Sinai Adolescent Health Center, 320 East 94th Street, 2nd floor, New York, NY 10128; email: angela.diaz@msnyuhealth.org tries to become expert care providers, leaders and advocates for teens. AHC staff members, including physicians, nurses, psychologists, social workers, health educators and nutritionists, serve as trainers and supervisors. Trainees include: medical students, residents, physicians, and graduate students from various programs, including nursing, social work, psychology, health education, health administration, and more. Finally, AHC staff integrates mentoring into its medical student and resident training programs.

In 1972, AHC began its Adolescent Medicine Fellowship program for individuals who have completed their residency in pediatrics, internal medicine, medicine/pediatrics or family practice and want to specialize in adolescent medicine. This program is currently one of about twenty accredited adolescent medicine fellowships in the country. (Adolescent medicine, a relatively new field, officially became recognized as a subspecialty in 1994.)

Center for Excellence

In 2000, AHC was designated one of two regional Centers for Excellence (CfE) in adolescent health by the New York State Department of Health. With a grant from the state, the CfE provides professional assistance and training to five community partnerships in New York State that promote youth development. CfE's professional assistance includes needs assessment and strategic planning; collaboration and partnership development; development of curricula for youth programs; and developing capabilities to perform self-evaluation of programs and services. In addition, CfE works with AHC clinicians on studies involving practice-based research.

Milestones

In 1968, AHC began its family planning program, and continues to provide reproductive health counseling and education to young women and men today. AHC established the first HIV/AIDS prevention program in 1987, which, five years later, received Ryan White funding for its mental health services to HIV-infected and HIV-affected youth. In 2003, AHC was designated as a Center of Excellence in HIV services by the New York State Department of Health AIDS Institute. In 2001, AHC received federal funding from the Substance Abuse and Mental Health Services Administration for its existing services to adolescents who have experienced trauma and to participate in a nationwide network of providers to increase and improve the exchange of knowledge concerning trauma services for teens.

Facts in Brief

Each year, AHC has more than 100,000 visits, of whom some 50.3% were Latino, 43.5% were African-American/Afro-Caribbean, 4.1% were White, 2% were Asian/Pacific Islander, and 0.1% were Native American. Approximately 50% of AHC clients reside in East Harlem and 50% come from northern Manhattan, the Lower East Side of Manhattan, the South Bronx, central Brooklyn, southeast Queens, and other communities in New York State.

AHC's core values produce outstanding results, which are measured by health outcomes, patient retention, and client satisfaction studies. These values include reducing barriers to service, building trust, treating clients with respect, encouraging parental involvement, maintaining confidentiality, offering age- and culture-appropriate services, providing support for risk factors like depression and substance abuse, and continuously reinvigorating AHC with the best practices in adolescent preventive medicine.

One excellent health care outcome with adolescents is having teen pregnancy rates that are lower than those for New York City, New York State, and the nation as a whole. The rate of pregnancy among AHC patients is 45% lower for African-American teens and 48% lower for Latino teens than in the broader teen population of New York City. AHC also has excellent outcomes in the prevention and treatment of sexually transmitted infections. Since 1985, rates of chlamydial infection among African-American and Latino patients have fallen from 28% to 7% and 24% to 4%, respectively, and the overall infection rates have dropped from 25% to 8.8%, with the lowest rates noted among continuing patients.

Fostering Resilience in Adolescent Females

Lorena M. Siqueira, M.D., and Angela Diaz, M.D.

Abstract

The health of adolescent females can be compromised by new social morbidities resulting from high-risk behaviors. The presence of various risk factors will increase the chances of their becoming involved in these behaviors and decrease their ability to reach the milestones of this developmental age. Protective factors will moderate these risks. Physicians and other health care providers can help foster resilience in the face of adversity by developing a better understanding of these factors and using a multidisciplinary approach to care.

Key Words: Adolescent females, adolescents, risk factors, protective factors, resilience.

During adolescence, the morbidity and mortality from infectious and communicable diseases declines, only to be replaced by new social morbidities stemming from high-risk behaviors such as eating disorders, sexuality, substance use and violence. In a survey on the health of adolescent girls, the Commonwealth Fund found that one in four girls exhibited depressive symptoms and that self-confidence and health ratings declined in high school for girls but not for boys (1). Thoughts of suicide among adolescent girls were reported to be alarmingly common.

Adolescent High-Risk Behaviors

While the average weight for women is on the increase, the ideal physique of the dominant culture tends to be slender. This contributes to various eating disorders among teenagers, such as increased dieting, especially by females. Inadequate intake of calories, protein, minerals and vitamins can have detrimental short- and long-term effects (2). Examples include a slower growth rate, delayed sexual maturation and a decrease in bone mineralization. And eating disorders may be associated with other risky behaviors, such as the use of cigarettes to control appetite and weight in the pursuit of thinness (3).

Unplanned and unprotected sexual activity results in about one million teenagers becoming pregnant every year (4). This high pregnancy rate mirrors the sexual activity rate in this population. While 22% of adolescent females are sexually active at age 15, 76% are having intercourse by the age of 19 (5). Other high-risk behavior such as drug use is associated with sexual activity, culminating in sexual intercourse; almost one in five sexually active teens report using alcohol and other drugs (6).

Alcohol is the addictive substance most widely used by adolescent females. In 1995, half of all adolescent students reported having consumed at least one drink during the previous month (6). Just under one third (28.6% of females) reported binge drinking (5 or more drinks on at least one occasion during the past 30 days) (6). The growth of tobacco advertising targeted toward young women, together with changing women's roles, has resulted in increasing rates of smoking among women (7). According to a 1997 report, the highest rates of smoking "in the past 30 days" were among white females and the lowest were among African-American females, with Hispanics somewhere

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in between. (1). Both genders reported similar personal and environmental reasons for smoking. However, there are gender differences in the personalities of adolescent smokers. Girls who are self-confident, outgoing, rebellious and socially skilled are more likely to be smokers, in contrast to adolescent male smokers, who tend to be more socially insecure (8).

During the past decade youthful violence, such as the recent school shootings by students, has received tremendous national attention. National surveys show that in 1995, 8% of females had carried a weapon in the past month and 5% had done so on school property. One out of three young women had been in a fight during the previous year (6). And homicides involving teens had increased 67% since 1978, and suicides 17% (6). The vast majority of the increase for both was due to gun violence.

More than one in five high school girls reported sexual or physical abuse in the 1997 survey (1). Most abuse occurred at home and occurred more than once, and the abuser was usually a family member. One in four girls had wanted to leave home because of violence. Abused girls often did not tell anyone about the abuse (48%) and talked to doctors about it only rarely (1). Nearly one in ten older girls reported abuse by dates or boyfriends.

Adolescent "Milestones"

As the fastest growing segment of the U.S. population comprises the minority ethnic and racial groups, those providing care to adolescents need to recognize how their health can be impacted by age and cultural values in addition to gender. Whatever their ethnic or cultural identity, however, adolescents tend to have common expectations, goals and values regarding the transition from childhood to adulthood. Adaptation during adolescence can be assessed by the achievement of the following milestones: (a) adjustment to pubertal changes, (b) some degree of separation from one's family, (c) achievement of economic independence, and (d) development of a stable self-identity and sexual identity. In the process of meeting these goals, individual differences in psychosocial health will influence their ability to overcome normal developmental hurdles and adversity. Psychosocial health implies both inner psychological well-being and "normal" external adaptation and adjustment.

Previously, the term "invulnerable" was used to describe a child who seemed to succeed despite the odds, in a particular situation. We now understand that this is a misconception (9). Everyone is at risk, although some individuals may be hardier than others. The individual's susceptibility will vary depending on the developmental phase she is in, the nature of the risk factor(s), the mechanisms by which the risk(s) operate, and the resources both within the individual and in the environment at that point in time.

Developmental Hurdles of Adolescent Females

The outcome of puberty is the achievement of adult physical stature and sexual dimorphism, and the development of secondary sexual characteristics and reproductive capabilities. Girls who mature early achieve physical maturity long before cognitive development is complete. The resultant pressure to act more mature than their age puts them at risk for engaging in various high-risk behaviors, and they may suffer the consequences. They often exhibit more dissatisfaction with their physical appearance, have lower self-esteem and show a greater degree of general unhappiness (10). It has been noted that in each successive decade over the last century, the age of onset of puberty and menstruation has been falling (11). Girls who mature late, on the other hand, appear to enjoy a possibly protective and psychological advantage from the immediate and extended environment, with familial support and a social network of peers of the same age or younger, and are less likely to engage in high-risk behavior (12).

For the adolescent, being different from his or her peers in any way is often interpreted as being abnormal. Concerns with pubertal changes of height, breast size and weight or the presence of acne can have a significant impact on self-esteem for any adolescent. In addition, various subcultures have their own concepts of beauty, and these may conflict with the dominant culture's view of beauty and attractiveness, and be protective or increase one's risk for problem behavior. For example, African-American females have a higher prevalence of obesity and show less discrepancy between their actual and ideal weights (13, 14).

A normal part of adolescent development is the experience of self-doubt and the need to test one's limits. Adolescence is a time of experimentation and exploring, to find a place for oneself in society. In the process of separating from one's family, the teenager moves into a peer group and may be influenced by their behavior. Qualitative changes in cognitive ability combined with the social expectations of women will also influence the adolescent female's decision making. While boys may separate easily from their mothers as they move through childhood and adolescence and learn to value autonomy, girls cherish intimacy and usually strive to remain in a relationship with their mothers (15).

Considerations in choosing to be financially independent are also influenced by social and cultural expectations. Our culture has historically devalued women and the qualities that it expects of them, such as nurturing, cooperation and intuition (15). Women who don't raise their children and men who don't support their families financially are often considered less than adequate. The expectation for women has been that fulfillment should come from taking care of the needs of others. The message is often given early in life with academic expectations. Girls may not be expected to do as well as their brothers or achieve as much, or they may be considered too competitive. Gender bias in the classroom has encouraged more assertive behavior in boys, who have also received more attention than do girls. Thus, only certain careers may be considered appropriate for her by her family, such as being a teacher or a social worker.

The contributions and experiences of girls and women are still sometimes considered marginal or are ignored in many of the textbooks used in schools (16). The curricula in schools often have lower expectations for girls in science and math, and give them the message that these should not be part of their future. Even girls who are highly competent in math and science are much less likely to pursue scientific or technological careers than are their male classmates (17).

Despite changing roles and greater equality of women in recent decades, girls today often fall into traditional patterns of low self-image, self-doubt, and self-censorship of their creative and intellectual potential. They emerge from adolescence with reduced expectations of themselves and have less confidence in their abilities than do boys. Without faith in their ability, physical desirability becomes central to self-image, which leaves girls vulnerable to sexual manipulation and other high-risk behavior (18).

Risk and Protective Factors That Influence Achievement of Milestones in the Face of Adversity

Resilience implies both good internal adaptation despite developmental risks and good external adaptation over time despite acute stressors or chronic adversities (9). Risk factors may be divided into two broad categories. The first is risks in the individual and his or her immediate environment. The second is risks in the social environment.

Individual risk factors or internal factors are related to physical and mental health. Physical health, genetic and prenatal influences, nutritional status and acute or chronic illnesses may all serve as risk factors. For emotional health, one's behavior and temperament, activity level and adaptability are areas of vulnerability. In their immediate environment adolescents have spheres of influence acting upon them, including the family, school and peer group. Factors in any of these areas may increase their vulnerability. For example, in the family sphere, discord and violence, lack of nurturing and communication, unclear expectations and poor monitoring of behavior, few and inconsistent rewards for positive behavior, parental emotional illness and/or substance use may all increase the adolescent's risk for problem behavior. School failure, lack of social skills and association with peers involved in high-risk behavior are other risk factors in their immediate environment.

The social environment includes the ethnic and cultural milieu in which the teenager grows up and the social expectations, norms and laws of the dominant society. For minority children, the interaction of social class, culture and race play a key role in determining patterns of socialization and developmental outcomes. For example, poor African-American children grow up in unique environments, and the problems and tasks which they need to gain mastery of can lead to the development of accommodations in cognition and behavior (19). Some of these behaviors, which are adaptive for survival on the street, will not serve them well when interacting with mainstream society. Also, success in meeting social expectations of behavior may exact an emotional toll, and it may be useful to differentiate between adaptive behavior and emotional health when looking at stress-resistant youth (20).

There are known risk factors in the individual, family and social environments, but there is no single factor or group of factors that will definitely predict one's risk. An imbalance between the demands on the person and the protective factors, which facilitate coping with challenges, may lead to poor functioning and stress. Not all risk factors can be eliminated or changed. The goal then is to moderate the effects of those risks which cannot be eliminated. The presence of protective factors will help reduce the impact of these risks.

Protective Factors

Mastering the developmental tasks of adolescence may be credited to individual factors such as self-regulation skills and cognitive functioning and also to effective parenting (21). Parenting styles that are sensitive, warm and consistently caring, but firm, have been associated with the development of self-control and compliance with social rules, whereas power-assertive methods of controlling a child's behavior (especially with hostile affect) generally have been associated with less compliance and less internalization of standards in children (22).

Some of the qualities of effective parenting are listed in Table 1. Providing opportunities for competence and confidence-building experiences will increase the chances that adolescents will successfully negotiate developmental hurdles (23). For those teens who do not have parental support, developing connections with competent adults other than their parents to build a supportive social network will also be protective. On the other hand, children and adolescents who are estranged from adults as resources and social references may lose valuable opportunities and sources of information (24).

Individual assets, in addition to cognitive skills and self-regulation, include having areas of talent or accomplishment valued by oneself and others; self-efficacy, self-worth and hopefulness; religious faith or affiliations and spirituality; socioeconomic advantages; adequate food and lack of anemia; physical fitness, endurance and vigor; and access to health care, decent schools and safe communities. Adolescents with these assets are more likely to resist negative peer pressure and be resilient in the face of adversity (23, 24).

TABLE 1
Effective Parenting Skills

Modeling competent behavior
Providing information and access to knowledge
Providing guidance and constructive feedback
Steering children away from wasteful or dangerous abilities
Supporting the taking on of new challenges
Functioning as advocates

TABLE 2
Individual Factors Contributing to Resilience

Insight (knowing)	The capacity to understand oneself with the development of empathy.
Independence (disengaging)	Distancing oneself at times of turmoil.
Relationships (recruiting)	Developing close and fulfilling ties to others.
Initiative (working)	Having goal-directed behavior.
Creativity (shaping)	This allows for self-expression and an outlet for pain.
Humor (shaping)	This lessens the impact of the trauma. One sees the comic in the tragic.
Morality (valuing)	The child surrounded by badness is imbued with a sense of goodness.

Reprinted with permission from Wolin SJ, Wolin S. The resilient self. How survivors of troubled families rise above adversity. New York: Villard Books; 1993 (25).

Using retrospective clinical data (see Table 2), Wolin and Wolin identified seven areas of strength or resilience that develop as children respond to troubles in their families, such as neglect, criticism, abuse or marital turmoil (25). These include developing insight or the capacity to understand oneself and others, with the development of empathy. This protects them, as it prevents them from internalizing the problems and generating guilt. Next is distancing themselves at times of turmoil, as they are developing independence. By doing so, they will be able to live apart as adults and relate to their families on their own terms. In addition, those who develop close and fulfilling ties to others who then serve as parent surrogates and friendship networks (i.e., relationships), tend to do better. Having goal-directed behavior helps them tackle problems later (initiative). Creativity allows for self-expression and an outlet for pain, and may lead to serious artistic endeavors. Humor lessens the impact of trauma; they see the comic in the tragic. Lastly, in developing moral values, the child surrounded by badness is imbued with a sense of goodness. This development of conscience leads ultimately to a sense of obligation to help or serve others.

There is interplay between individual and family factors. For example, children who are less adaptable or are hyperactive and impulsive may experience less parental support and develop a repertoire of less effective coping strategies. When they enter adolescence and are faced with challenges in the academic or social arena, they may deal with situations less effectively. They may respond with anger or helplessness, turn to non-normative peers and use high-risk behaviors as a means of coping (26). Adolescents in whom there is an imbalance between risk and protective factors may engage in high-risk behaviors, which can impact on their physical and mental health. This in turn may ultimately interfere with their ability to achieve developmental milestones.

Fostering Resilience—Recommendations

Helping our adolescents successfully negotiate the path to adulthood is necessary for a healthy society. The need for regular visits to the pediatrician in the first five years is widely accepted. The need for health supervision after this time is less appreciated. In addition, access to health care during adolescence is limited by the lack of insurance coverage, high health care costs and girls' reluctance to seek care. They may be too embarrassed or afraid to discuss a problem with the health care provider or they may not get the opportunity to talk privately with the doctor (1).

Improved knowledge of normal growth and development during adolescence will help health care providers expand the scope of delivered services. Providing this information in a nonjudgmental fashion with reassurance and support when the adolescent needs it, is key. The availability of a caring professional who is willing to listen and help them prioritize their goals can be extremely helpful for girls if they are to develop self-worth and self-efficacy, and reduce stress.

Primary prevention, care that is given to prevent the onset of a condition, usually includes providing anticipatory guidance. An understanding of normal milestones leads to anticipation of normal physical and developmental changes, with anticipation of related problems. Physicians should engage in discussions of how one can avoid or handle these problems or can cope with inevitable changes, such as by discussing breast development and menses before they occur, in order to reduce anxiety. Similarly, discussions of stressors such as school transitions or going away to college, assist with adjustment. An extension of this anticipatory guidance is the need for health care providers to foster resilience by determining their patients' possible risk and protective factors during adolescence, thereby helping them to decrease risk, enhance protective factors, recognize and enhance their strengths, and adopt the best coping strategies (27, 28). Table 3 presents the typical personality traits of resilient children.

Parental skills training should focus on helping parents nurture and guide their children's behavior, use appropriate limit setting for undesired behavior and consistently reward pro-social behavior. During adolescence, parents and other adults need to encourage young women to be individuals and not just followers in the crowd. Adolescents need to be taught life skills and thus develop self-efficacy and the ability to resist peer pressure (29). Parents should maintain high expectations for their daughter's schoolwork, extracurricular activities, athletic participation and other hobbies. The message should be clear that gender does not excuse them from the pursuit of excellence and that having goals helps young people stay on track.

The role of extracurricular activities in the development of competence and self-esteem needs further investigation. The hope is that more such involvement will help teenagers develop self-esteem and the ability to resist gangs, drugs and other violent activities. Boredom, lack of supervision and the lack of availability of adults for discussions of concerns all contribute to experimentation with high-risk behavior. One of the keys to successfully overcoming these challenges and feeling good about oneself is the ability to get reliable information from a trusted adult. Parents and teachers need to be reminded that their adolescent females' views and feelings need to be validated as much as those of their adolescent males.

The fact that physical and mental health are linked is often not communicated to our adolescents. They should be taught that a balanced diet with adequate calories, adequate sleep and regular exercise improve endurance and help

TABLE 3
Personality Traits of Resilient Children

Well-developed sense of self
Positive orientation to one's surroundings
Internal locus of control
High self-esteem
Superior social skills
Sensitivity
Adaptability and flexibility

reduce feelings of stress. Adolescence is a challenging time for both males and females. However, young women report one-third more emotional distress than do young men. The mixed emotional signals they receive from their environment may contribute to this.

It is better for adults to demonstrate safe behavior than for them to preach it. The need for the use of seat belts and bicycle helmets, wearing protective gear during sports, drinking in moderation, and not drinking and driving are some examples. If there are guns in the house, the need to store the guns and ammunition separately needs to be actively practiced and enforced (30).

Girls whose parents are willing to discuss sex, set firm rules, clearly communicate their beliefs and values, and provide accurate information are more likely to avoid sexual activity, pregnancy, and sexually transmitted diseases (31, 32). Parents often fear that talking about sex will promote sexual activity, or they may be uncomfortable with their lack of knowledge in some areas. Parents should be reassured on both counts. They can be encouraged to search for information together. Girls need to know that their curiosity is normal, and asking questions should be encouraged.

Independent of parents' own abstinence from drugs, the message should be clear that the use of drugs is life threatening. Experimentation can lead to continued use and abuse, and chronic drug use is a disease that is difficult to cure. Prevention of substance use entails more than discussion of short- and long-term side effects. Promoting individual social competence, in addition to specific skills for resisting the social and environmental pressures to initiate substance use, is needed (e.g., decision making, self-image improvement, communication skills, and assertiveness) (29).

A multidisciplinary approach to health care delivery is optimal. Health educators have the time and expertise to provide adolescents with knowledge and information on the consequences of high-risk behavior, and to guide them to avoid involvement or reduce the risks, with behavior modification. Mental health professionals can provide individual and family therapy, which will help the adolescent deal better with problems and improve coping skills. For those with chronic illnesses or specific mental health problems (e.g., victims of incest), group therapy can be a very effective model for intervention and support. More in-depth therapy or psychiatric intervention can be provided as needed. Helping teens gain access to housing, food, transportation, or school enrollment, as needed, will also reduce their level of stress. For the adolescent who could benefit from a mentoring relationship, a caring and supportive one should be developed.

Finally, physicians should be willing to use their standing in the community to advocate for better schools, safer playgrounds and neighborhoods, more after-school activities, improved health care and insurance coverage, and greater access to care.

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Nutrition and Eating Disorders in Adolescents

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Abstract

Adequate nutrition is essential during adolescence, since growth and development during this period play key roles in achieving normal adult size and reproductive capacity. This article briefly reviews recommended caloric intake; the healthy balance of carbohydrates, fat and protein; and the appropriate dietary intake of iron, folic acid and calcium for the adolescent. A major potential obstacle to good nutrition for an adolescent is the development of an eating disorder such as anorexia nervosa or bulimia nervosa. Anorexia nervosa, characterized by severe underweight, fear of gaining weight, and low self-esteem and amenorrhea, is associated with many physiological and psychological complications with which the provider must be familiar. Similarly, bulimia nervosa, which presents with eating binges followed by compensatory behaviors such as vomiting, diet pill abuse and overexercise, may be harder to detect, but can also have devastating consequences, both physically and emotionally, for a young person. Both of these disorders are best treated by a multidisciplinary team of specialists to address the medical, psychological, and nutritional components of these illnesses.

Key Words: Adolescence, nutrition, anorexia nervosa, bulimia nervosa, eating disorders, adolescent health.

Introduction

ADOLESCENCE IS A TIME of major growth and development, and nutrition plays a key role. The adolescent growth spurt accounts for approximately 25% of adult height and 50% of adult weight (1). In addition, adolescents are developing reproductive capacity at this time. Nutritional intake has to support this growth by providing not only enough energy, but also the proper balance of protein, carbohydrates, fats, vitamins, and minerals. This article will briefly discuss the basic nutritional requirements for adolescents as well as two common eating disorders that can affect the health of adolescents: anorexia nervosa (AN) and bulimia nervosa (BN).

Nutritional Requirements for Adolescents

While Recommended Daily Allowance (RDA) standards for adequate nutrition have been developed for the average adult, no such specific standards have been defined for the growing, developing adolescent. Therefore, nutritional recommendations should be viewed as general guidelines and should be adjusted for special conditions such as a significant growth spurt, athletic participation, major stress, or a chronic illness. According to one source, caloric needs for adolescents, ages 11 – 14 and 15 – 18, are 47 kcal/kg and 40 kcal/kg, respectively (2). It is generally accepted that, of this total, 55 – 60% should be derived from carbohydrates and less than 30% from fat (with less than 10% from saturated fat). The recommended protein intake for adolescents 11 – 14 years old is 46 g (1 g/kg body weight) and for those 15 – 18 years old is 44 g (0.8 g/kg body weight) (3).

It is beyond the scope of this article to review every nutrient and its value to the health of the teenage patient; however, certain vitamins and minerals merit discussion. For example, calcium is a mineral that is essential for maximizing the length and density of growing bones, and this growth process reaches its peak during the teen years. Inadequate intake of calcium during these "opportunity" years may lead to osteoporosis later in life, particularly in fe-

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males. The most recent recommendation for daily calcium intake from the first Dietary Reference Intake (DRI) report is 1300 mg/day (4). Unfortunately, representative groups of adolescent females surveyed during the period 1980 – 1992 had a daily calcium intake approximately 100 – 125 mg below the average intake estimated from other national studies, and even further below the recommended daily allowance (5). While it may be necessary to prescribe supplements for adolescent patients who are not consuming adequate calcium, it would be more beneficial for them to consume calcium in the form of foods, which can provide additional nutrients as well.

Iron and folic acid are two other nutritional factors commonly deficient in adolescent females. Anemia, most commonly the result of iron deficiency, is defined as a hemoglobin level of less than 11.8 g/dL at ages 12 – 14.9 years and less than 12.0 g/dL at ages 15 years and older (6). Iron is derived from two primary sources: heme iron, from animal products, and non-heme iron, from vegetable sources. Moreover, iron absorption is improved with concurrent intake of vitamin C and inhibited by ingestion of fiber, phytates, and phenols (e.g., in tea). Screening for iron-deficiency anemia should be done for all menstruating females. Folic acid deficiency is the second leading cause of nutritional anemia in adolescents. Folate is derived from liver, yeast, leafy vegetables, legumes and some fruits; however, routine household preparation may destroy up to 50% of the folate present in foods (7). Folate supplementation has recently been demonstrated to be beneficial prior to and during pregnancy, resulting in a lower incidence of birth defects and low-birth-weight infants (8).

While adolescents require adequate intake of vitamins and nutrients in order to grow and develop to their full potential, they may not always choose the appropriate foods to accomplish this. Food choices may parallel adolescent development; that is, just as the younger child or early adolescent is still very much influenced by his family, so too are food choices. But as the adolescent grows older and more independent, other factors may become more influential. For example, in an era when many parents are working and dining out is common, older teens are frequently responsible for their own meals. Neumark-Sztainer and colleagues found that the most influential factors in the adolescent's food selection included hunger or cravings, taste of food, time available, and convenience of food (9). With the busy schedule of so many teens, fast food and vending machines are often the answer to meal and snack preparation. Unfortunately, these foods, which are high in sugar and fat, account for a significant amount of the daily calories. Other considerations in food selection include mood, body image concern, cost, vegetarianism, and ethnicity. In addition, the media provides exposure to different types of foods and also tends to present thinner body types as "ideal." In this regard, television and magazines have been shown to have considerable influence on female adolescents' eating habits (10, 11). Teens are a vulnerable population for a lucrative market, and advertisers in the media often target specific campaigns directly at them. Finally, peers influence the dietary selection of an adolescent: they set standards for acceptable food habits, dining location, and even timing of meals. Chapman and Maclean surveyed a group of Canadian adolescents aged 11 – 18 years to learn their emotional associations with particular foods, and found that "junk food" was associated with pleasure, overeating, independence, guilt, and loyalty to friends. On the contrary, "healthy food" was associated with family, meals, and being at home (12).

Eating Disorders in Adolescents

While dieting behaviors have become widespread among teenagers in the United States (13), it is not clear why only some of these teenagers develop eating disorders. Cultural messages glorifying thinness certainly play a large role in creating the pressure that an individual feels to lose weight. Moreover, self-esteem has been shown to fall in early adolescence, particularly in young girls, making them vulnerable to dissatisfaction with their own bodies (14). Biological factors may also be responsible for increasing the probability of developing eating disorders among adolescent females. Studies of both families and twins, for example, suggest a genetic predisposition for the development of eating disorders (15). The likely target of the proposed genetic coding is in the serotonergic pathway (16). Considerable evidence is mounting that patients with either anorexia or bulimia have elevated serotonin metabolites in their cerebrospinal fluid, and that this seems to correlate directly with the severity of symptoms (16 – 18).

Anorexia Nervosa

Once described by Hilde Bruch as the "relentless pursuit of thinness" (19), anorexia nervosa (AN) is a disorder that plagues approximately 0.5–1% of adolescents (20), fewer than 10% of whom are male. The diagnostic criteria have evolved into those described in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders*, summarized in Table 1 (21). The intensity of the fear of weight gain and the fear of lack of self-esteem are what make this condition so very painful for the young patient. In addition, she is likely to have certain personality traits such as being a perfectionist, obsessive-compulsive, socially withdrawn, high-achieving (but rarely satisfied), and depressed. The patient with AN may be exclusively restricting dietary intake (restrictive sub-type) or may experience episodes of binging and purging (bulimic sub-type) (21).

Diagnosis of the adolescent with AN is rarely simple. A patient may present with various vague complaints, such as weakness, dizziness, fatigue or occasionally amenorrhea. Frequently, she is coerced into seeking medical attention by a distressed parent. An appropriate history includes questions gently asked about how the patient feels about her weight, specific methods of weight loss, and the patient's own weight goals. Teenagers suspected of having AN should be asked about meal patterns, depression, family interactions, and other more general psychosocial issues such as functioning at school and peer interactions. General medical history questions can help to rule out organic causes of weight loss, such as hyperthyroidism or inflammatory bowel disease.

TABLE 1
Diagnostic Criteria for Anorexia Nervosa

1. Refusal to maintain weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
2. Intense fear of gaining weight or becoming fat, even though underweight.
3. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
4. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen administration.)

Specify type:

Restricting Type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Binge-Eating/Purging Type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

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Once historical information suggests a possible diagnosis of AN, a complete physical examination should be performed. Patients become skillful at masking their low weight, frequently dressing in baggy clothing or overloading with fluid prior to being weighed. It is therefore important to obtain the patient's weight after obtaining a urine specimen (for measurement of specific gravity), when she is wearing only a gown and underwear. The most precise quantification of weight and body composition is often debated in the literature (22); however, the most frequently used measure is the body mass index (BMI), which is the weight (kg) divided by the height (m) squared. A BMI of less than 18 is consistent with a diagnosis of AN. Careful assessment of vital signs is important to rule out hypotension, bradycardia, orthostasis and hypothermia. In addition, examination of the skin for lanugo hair, carotinemia, or Russell's sign (calluses on the knuckles) can be revealing. A cardiac examination and ECG are helpful in detecting either low voltage or arrhythmia, which may be seen in the patient with AN. Laboratory evaluation includes electrolytes; a complete blood count; thyroid function tests; hormonal work-up of amenorrhea; and levels of certain minerals such as calcium, iron, zinc, phosphate, and magnesium. An erythrocyte sedimentation rate can be helpful in ruling out a chronic inflammatory condition, since it is characteristically very low in the patient with AN.

Once the diagnosis of AN is strongly suspected, the primary practitioner will essentially become the coordinator of the multidisciplinary treatment team. That is, while the patient is monitored medically, she will also benefit from an evaluation by a nutritionist and by a mental health professional. The nutritionist is consulted to assist with caloric and nutritional assessment, food diary instruction, nutritional education, and menu planning. The mental health professional is involved to explore underlying emotional issues as well as to utilize more immediate behavioral approaches to increase the patient's comfort with eating and maintaining normal body weight. In addition, a psychiatrist may be consulted to prescribe medication. Antidepressants such as the selective serotonin reuptake inhibitors may be effective for the teenager with AN, particularly when depression or obsessive-compulsive behaviors are prominent.

A major treatment goal is optimal management of the patient's amenorrhea. Amenorrhea in the patient with AN is thought to be a result of the severe caloric restriction, which suppresses the hypothalamic-pituitary axis (23). Biochemical mediators of this process that have been implicated include cortisol, leptin, growth hormone and insulin-like growth factor I (24–27). All of these mediators may play a role in the process. Regardless, the result is a suppression of the pituitary gland's production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Without normal cycling of LH and FSH, there is a very low circulating level of estrogen and no ovulation. The amenorrhea which results may be desired by the patient, particularly if she is seeking to remain "young," or it may be of concern to the patient and may be the reason she seeks medical attention.

Because of the amenorrhea, the adolescent with AN is at risk for developing osteoporosis. Although the pathophysiology of osteoporosis is not well understood, it is known that adolescence is a critical time for bone mineralization and that estrogen appears to play a major role in this process (28). Therefore, having low estrogen levels and amenorrhea at this time represents a significant "missed opportunity" for bone formation. This results in risk of fracture, not only later during the post-menopausal period, but also prior to menopause. In fact, because the patient with AN frequently exercises strenuously, she may be prone to stress fractures, even during adolescence. In the female athlete, this combination of menstrual disorders, eating disorders, and osteoporosis has been termed the "female athletic triad" (29).

Treatment regimens including hormonal and nutritional manipulation have been studied to assess their impact on bone mineral density. Although some studies have not demonstrated significant benefit from either calcium or estrogen supplementation (30), one study of combined oral contraceptive pills along with calcium supplementation for at least 12 months demonstrated improvement (although not normalization) of bone density (31). Treatment with androgens is another modality under consideration (32). The only intervention that has been shown to be effective in restoring bone density, however, is regaining body weight, and even this may not restore bone to its full potential (33).

If initial assessment of a patient reveals that she is either medically or psychiatrically unstable (or if she has failed outpatient treatment), she must be hospitalized. Inpatient programs that incorporate both medical intervention and structured behavior modification techniques tend to be most successful, but may not always be available because of geographic and/or financial obstacles. Day treatment is also of value in the management of patients with AN, as it provides an opportunity for structure and support during the day, yet allows the patient to continue residing in her usual environment.

The prognosis for the teenager with AN is guarded. Outcome studies are often difficult to compare, as different parameters of "success" and "failure" may be used. However, one summary of 68 outcome studies concluded the following: approximately 40% of anorexic patients recover, approximately 35% improve but continue to struggle over weight issues, and 20% suffer a chronic, severe course (34). There is a 5% mortality rate, which is the highest mortality rate of any psychiatric diagnosis. Characteristics associated with a poor prognosis include delay in diagnosis and treatment, relatively high degree of weight loss, bulimic symptoms, and certain personality traits such as low self-esteem, impulsiveness, and interpersonal distrust (34). Therefore, it is helpful both for the medical provider and the patient to understand that this is a chronic illness and to set reasonable goals and expectations for treatment.

Bulimia Nervosa

Bulimia nervosa (BN) is considerably more common among adolescents than is AN. Estimating the prevalence of BN is more difficult, however, because diagnosing this disorder requires that the patient admit to behaviors about which she probably feels great shame and guilt. Nevertheless, studies have estimated that the prevalence is on the order of 1–5% of adolescents (35), with the highest risk among female college students (36, 37).

Just as the diagnostic criteria of AN have undergone redefinition over the years, so too have those of BN. The current diagnostic criteria are detailed in Table 2 (21). Whereas the prominent feature of AN is the caloric restric-

TABLE 2
Diagnostic Criteria for Bulimia Nervosa

1. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   a. eating in a discrete period of time (e.g., within any 2-hour period) an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
   b. a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
2. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.
3. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.
4. Self-evaluation is unduly influenced by body shape and weight.
5. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify type:

Purging Type: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

Nonpurging Type: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.

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tion and resulting underweight, the prominent elements of BN are the episodes of binge eating (eating large amounts of food, with a lack of control) and the compensatory behaviors which follow, of a patient who is either of normal weight or overweight. The compensatory behaviors include self-induced vomiting, laxative abuse, diuretic abuse, overexercise, caloric restriction, and diet pill abuse. Usually the patient suffers painful remorse after these behaviors, but is unable to control the impulse to repeat them. A young woman with BN characteristically has low self-esteem, is depressed and/or anxious, and has poor impulse control. She typically engages in many other risky and self-destructive behaviors, such as substance abuse, unprotected sexual activity, self-mutilation, and suicide attempts.

Because the adolescent with BN experiences a great deal of shame and becomes very practiced at masking her behaviors, it is challenging to diagnose this disorder. Eliciting a history is crucial, and it may be that the patient will reveal her history only after much time has passed and the medical provider has been able to gain her trust. Once the diagnosis of BN is suggested, details of the frequency and caloric contents of the binges as well as the methods of "purging" must be obtained. Binges may only follow periods of caloric restriction, so a complete food recall must be attempted with the patient. Because vomiting and laxative abuse may result in electrolyte abnormalities and dehydration, patients must be asked about dizziness, palpitations, and weakness. Just as with the patient with AN, a full medical and psychosocial history should be obtained. Menstrual irregularity is also common in a patient with BN.

Medical examination of the adolescent with BN should be performed with particular attention to ruling out consequences of severe binging and purging behaviors. Vital signs and hydration status are essential when assessing acuity. Dentition may be poor from repeated vomiting, although it is generally only after 2–3 years of vomiting that the dental enamel will become eroded. Gastritis and constipation are common with vomiting and laxative abuse, respectively. Russell's sign (calluses) may be seen on the knuckles. Important tests to be done in the initial assessment of the patient are an ECG, and determination of serum electrolytes to rule out hypokalemia, hyponatremia, and metabolic alkalosis. These disturbances are not uncommon and may trigger dangerous arrhythmias in these patients. A complete blood count, thyroid function tests, and perhaps hormonal assessment if menstrual irregularity is present, may also be performed.

Treatment of patients with BN is coordinated in much the same fashion as that for patients with AN; that is, with a multidisplinary team comprised of the medical provider, nutritionist, psychotherapist and possibly a psychiatrist. Because the adolescent with either eating disorder may be quite skillful at manipulating the individual team members, the treatment team will be most effective if the providers formulate specific treatment goals and plans, and communicate on a very regular basis. Likewise, the team should establish hospitalization criteria early in the treatment to avoid any ambiguity; however, hospitalization is less frequently necessary for patients with BN than for those with AN. Day treatment is an option for patients who are not functioning well, but who are stable enough medically not to require hospitalization.

Because eating disorders in general and BN in particular have little to do with hunger and food, and much more to do with coping with stress, much work with these patients has focused on the emotional triggers of the binge/purge cycles. While traditional therapy has centered on the patient's past, current trends are concentrated on the present. Cognitive behavioral techniques allow the patient to identify stressors or triggers of binges, to use either relaxation and/or cognitive techniques, and then to channel emotions into a more constructive behavior. Alone, or in combination with an anxiolytic or antidepressant medication, these newer techniques have been shown to be very effective in improving the outcome for adolescents with BN (38).

The data concerning the outcome of treatment for BN is difficult to obtain and few long-term studies are available for review. Nevertheless, it appears from the few studies that are available, that with treatment, about 50% of patients will recover from BN, 30% will have occasional bulimic behaviors, and 20% will continue to have the full disorder (39). Factors associated with a more favorable prognosis include shorter duration of symptoms and no diagnosed personality disorder (39).

Binge Eating Disorder

In recent years, practitioners have become aware of an eating pattern of binge eating without the compensatory behaviors or purging. This entity, termed "binge eating disorder," is still being investigated, but it has achieved diagnostic status in the current *Diagnostic and Statistical Manual of Mental Disorders* (21). As with bulimia, patients frequently binge in reaction to a stress rather than because of actual hunger, and their binge patterns are similar to those of patients with bulimia. Teenagers with this syndrome may seek help for weight loss without disclosing the nature of their overeating. It is therefore important to ask all of these patients about eating patterns as well as total amounts and the nature of the foods. Because binge eating disorder has only been described recently, it is not yet clear how best to treat these patients.

Conclusions

Because of all the developmental changes adolescents are experiencing or have so recently experienced, they are very sensitive about body shape and appearance. And their nutritional intake and food choices are important both for their growth and development and their future health. In addition, this is a time when the adolescent female in particular may be vulnerable to external pressures to be thin, and she may react by either trying to control her dietary intake to an extreme or by using food as a way of coping with stress. The medical provider can help the young patient by asking about daily food intake and feelings about weight, and by providing guidance and even reassurance when a patient is "normal." In addition, if a problem is detected, appropriate referrals for intervention can improve the adolescent's outcome dramatically.

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Adolescents and Immunization:

Tips for the Primary Care Provider

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Abstract

Despite high immunization rates in this country, many adolescents do not receive all of the recommended vaccines. Each year, more than 3.5 million adolescents in the U.S. enter adulthood lacking recommended immunizations. This article will review the current recommendations for immunization for adolescents, including those for the meningococcal vaccine. The vaccine schedule is continually changing, and it is important that health care providers be up to date and utilize available resources with current information. Primary care providers should review and update immunization records with their adolescent patients on a routine basis.

Key Words: Adolescence, immunization, vaccination, adolescent health, ethics.

IMMUNIZATION PROGRAMS have had a major impact on the morbidity and mortality of many diseases. Although infant and childhood immunization rates in the United States are higher than ever, many adolescents do not receive all of the recommended vaccines. It is estimated that every year in the United States more than 3.5 million adolescents enter adulthood lacking some recommended immunizations (1). Primary care providers should review and update immunizations at all encounters with adolescents, whenever feasible, to avoid "missed opportunities" for vaccination.

In 1996, the Advisory Committee on Immunization Practice (ACIP), the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AFP) and the American Medical Association (AMA) issued a consensus statement emphasizing the importance of a routine well adolescent visit at age 11 – 12 years. At this visit, the primary care provider would review the adolescent's immunization history and administer all missing vaccines, including the vaccines for hepatitis B, and varicella if clinically indicated (2). In addition, a booster tetanus and diphtheria toxoid (Td) vaccine would also be given as well as a second measles, mumps, and rubella vaccine (MMR) if the second MMR vaccine had not already been given. Presently, the American College Health Association (ACHA) mandates immunization against hepatitis B, varicella, diphtheria, and polio prior to college entrance (3). The ACHA also recommends vaccination against *Neiserria meningitidis* (3). Since the vaccine schedule is frequently modified, it is critical that all health care professionals providing care to adolescents be aware of the current recommended guidelines.

Hepatitis B

In the United States, 70% of the estimated 100,000 – 140,000 annual cases of hepatitis B infection involve adolescents and young adults (4). Approximately 5 – 10% of adolescents and young adults infected with hepatitis B become chronic carriers and therefore are at risk of developing chronic liver disease (5). The majority of cases of hepatitis B in adolescents result from sexual intercourse and intravenous drug use. Previous immunization strategies targeted at "high risk" groups have been unsuccessful in eradicating hepatitis B. Consequently, the ACIP and the AAP recommend vaccination of all children and adolescents against hepatitis B.

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All unvaccinated adolescents should receive 3 doses of hepatitis B vaccine, adhering to the manufacturer's dosing schedule. These patients should receive the first dose of the vaccine as soon as possible, following a schedule of 0, 1 month and 6 months. An alternative schedule has been proposed, with dose 1 given as soon as possible, dose 2 given at least 1 month after dose 1, and dose 3 at least 2 months after dose 2 and 4 months after dose 1. It is believed that 50% of adolescents will have protective antibody levels after dose 1, 70% after dose 2, and over 90% after three doses (6). The two currently available vaccines against hepatitis B for adolescents and adults are Recombivax (Merck & Co., Whitehouse Station, NJ) and Engerix-B (SmithKline Beechum Biologicals, Research Triangle Park, NC). Both are very immunogenic, producing seroprotective levels of antibody in at least 97% of infants and children after three doses of the vaccine. The vaccines are also interchangeable, and protective immunogenicity has been found to be comparable when patients received both Engerix-B and Recombivax to complete their series. It is important for the primary care provider to remember that it is not necessary to restart the series, no matter how much time has elapsed between doses. For example, if a patient presents for hepatitis B vaccine dose number 2 six months after receiving the first dose, dose 2 should be given then, with dose 3 separated by an interval of at least 2 months to complete the series. For adolescents 11–15 years old, there is also a 2-dose schedule available for Recombivax using the adult dose (10 mcg) separated by 4–6 months (7).

Diphtheria, Tetanus, Pertussis

Routine immunization should continue at age 11–12 years with a Td (tetanus and diphtheroid toxoids) booster; a Td booster should be given every 10 years throughout life.

At this time, routine vaccination for pertussis is not recommended for children over the age of 7 years. However, a recent study conducted by the National Institutes of Health may support the addition of an acellular pertussis vaccine to the current Td booster for adolescents (8).

Polio

Before vaccines for polio were available, there were 13,000–20,000 cases of paralytic polio in the United States every year (9). Polio vaccines have led to the eradication of wild type polio in the United States and the Western Hemisphere. The World Health Organization (WHO) reports that in 1997 only 5,160 cases of polio were reported; the effort continues to eliminate polio worldwide.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) has revised the immunization recommendations for polio; in January 2000 an inactivated polio vaccine (IPV) for childhood immunization was recommended (10). This change was made because of the small risk that vaccine-associated paralytic poliomyelitis could occur after receiving the oral polio vaccine (OPV). Because there have been no recent cases of poliomyelitis in this country, the ACIP feels that the risk-benefit balance of using OPV in this country is unacceptable.

As of January 2000, all children need to receive 4 doses of IPV: at the ages of 2, 4, and 6–18 months, and at 4–6 years. For travel to polio-endemic areas, a decision to use either OPV or IPV can be made based on the child's previous immunization status and time before departing for the other country. However, OPV remains the preferred vaccine for mass immunization programs to control polio in polio-endemic countries (10, 11).

Measles, Mumps, Rubella

Use of the measles vaccine has led to a more than 95% reduction in measles. However, the measles virus is still prevalent in many parts of the world. WHO estimates that 1.1 million deaths in the world were caused by measles in 1995 (9). There was a major epidemic of measles from 1989-1991 in the United States, resulting in 11,000 hospitalizations and 120 deaths (9). This epidemic was largely attributed to low rates of immunization against measles in pre-school children.

Rubella is usually a mild disease in children and adults. However, rubella in pregnancy can have disastrous effects on the developing fetus. Rubella infection of a pregnant woman can cause congenital rubella syndrome in the fetus, which consists of mental retardation, cardiac lesion, neurologic impairment and eye deformities. Because there is a theoretical risk to the fetus, measles, mumps, rubella vaccine (MMR) should not be given to an adolescent who is known to be pregnant or considering becoming pregnant in the three months after receiving the vaccine (3). However, there is no direct evidence that giving MMR to a pregnant woman will harm the fetus (3).

Mumps is caused by a paramyxovirus and causes a systemic illness often accompanied by salivary gland swelling. In adults the infection is usually more severe; thus, it is more likely to cause orchitis in men than in boys.

Routine immunization for measles, mumps and rubella is recommended for all children at 12 – 15 months of age. In addition, a second dose of MMR should be given when a child enters school (at ages 4 – 6) . Children who have not received two doses of MMR should complete the series by early adolescence.

MMR is a live virus vaccine and therefore should not be given to severely immunocompromised individuals, including those with AIDS. There has been one report of the vaccine causing fatal disease in a patient with AIDS and severely depressed lymphocyte counts (12). Furthermore, individuals with severe immunosuppression are less likely to mount a protective antibody response after immunization (12). Therefore, the AAP does not recommend routine immunization with MMR for severely immunocompromised individuals with HIV, as defined by CD4 counts and total lymphocyte counts.

Varicella (Chickenpox)

The varicella vaccine was licensed by the Food and Drug Administration (FDA) in March 1995 and added to the recommended immunization schedule in 1996. It is estimated that 3.5 million cases of varicella occurred in the United States between 1980 and 1995 (13, 14). Approximately 90% of the cases in that period involved children 12 months to 14 years of age, with the highest incidence among school age children 5 – 9 years old (13, 14). From 1985 – 1990, there were more than 8,000 chickenpox-related hospitalizations in the United States (13, 14). The CDC estimates that only 26% of the nation's susceptible two-year-olds have been vaccinated for varicella.

The varicella vaccine (Varivax, Oka/Merck & Co., West Point, PA) is a cell-free, live-attenuated preparation derived from the Oka strain of the varicella virus. One dose of the varicella vaccine is recommended for universal immunization for children 12 – 18 months old, provided that there has been no previous history of varicella, or for immunization of susceptible individuals 19 months to 12 years old. For healthy adolescents and young adults, two doses of the vaccine are recommended, separated by an interval of 4 – 8 weeks, provided there has been no previous history of varicella or Varivax vaccine. The "catch-up visit" at age 11 – 12 years is an excellent opportunity to review the patient's history of varicella and to immunize against varicella when indicated. Varicella can be more serious in adolescents and adults; therefore, vaccination of susceptible adolescents and adults should be encouraged.

Varivax should not be given to a woman who is pregnant, since it is a live virus vaccine. However, there is no evidence that this vaccine poses any harmful risks to the developing fetus (3, 15). The Centers for Disease Control (CDC) and Merck pharmaceutical company maintain an active worldwide vaccine registry for women who inadvertently received the varicella vaccine during pregnancy. To date, there have been no cases of congenital varicella syndrome in the offspring of these women (3, 15).

Meningococcal Vaccine

The ACHA and the AAP recommend the meningococcal vaccine for all college students (3, 8). In addition, the CDC recommends vaccination for college freshmen, especially those living in dormitories. Data from the CDC for the 1998 – 1999 school year, for college students living on campus, show an increased risk for contracting meningococcal disease (8). The meningococcal vaccine contains the purified polysaccharide of four serogroups of *Neiserria meningitidis*: A, C, Y, and W-135 (3). The meningococcal vaccine does not, however, protect against serotype B, which is responsible for about one-third of the cases of meningococcal disease, according to a recent CDC study (8). This vaccine is given subcutaneously as one dose, with protective levels of antibody reached approximately 1 week after vaccination. Health care providers should counsel their adolescent patients who will be entering college and those already in college, about this vaccine.

Conclusion

Although pediatric immunization rates are higher than ever, there is still much work to be done. All health care providers should review and update the immunization histories of all their patients at all encounters. Vaccine registries that are rapidly accessible to providers will greatly help in assessing immunization status. Furthermore, since new vaccines are introduced into the schedule periodically, it is imperative that health care providers review the relevant literature on immunizations and implement whatever is recommended and necessary.

It is imperative that all health care providers have access to and utilize national organizations to keep abreast of all the new developments in the field. Moreover, as the number of injections necessary for routine immunization continues to increase, it is critical that providers discuss the importance of vaccination with adolescents and their families, and form close partnerships with the communities they serve.

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Foster Children with Special Needs:

The Children's Aid Society Experience

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Abstract

Children in foster care have many health needs. This article presents the model of the Children's Aid Society (CAS) of New York City in addressing these needs. In addition to their regular foster care program, CAS developed the Medical Foster Care (MFC) in response to the growing number of boarder babies (children with medical conditions who are abandoned at hospitals), and the Therapeutic Foster Care (TFC) for foster children with emotional and behavioral mental health problems. The MFC serves 145 children considered medically fragile, as evidenced by congenital diseases such as heart disease, renal agenesis, cerebral palsy, seizure disorders and mental retardation. The TFC serves 50 children with severe levels of emotional and behavioral symptomatology. As is indicated by the extensive services offered through CAS's regular foster care program, as well as MFC and TFC, these children require specialized treatment. In addition, systems of information maintenance and exchange surrounding the health care of foster children need to be improved. Often agencies are ill-equipped to do adequate background checks on these young people and as a result deliver them to foster care situations where their health needs are not revealed and therefore not addressed. Health care providers also need to stay informed on the overall subject of foster care, as their voices will probably be crucial in ensuring that the extensive needs of these children are adequately represented to government, medical and other service providers.

Key Words: Foster care children, foster care adolescent health, Children's Aid Society.

Introduction

Some of the unhealthiest children in the United States are those in foster care (1). Dr. Paula Jaudes of the University of Chicago states that foster care children are twice as likely to have chronic diseases and 4.5 times as likely to have psychological illnesses when compared with children involved with the Aid to Families with Dependent Children (AFDC) program (1). Studies from the General Accounting Office indicate that as many as 58% of foster care children have serious health problems and 62% have been subject to prenatal drug exposure (2). Further studies from the Child Welfare League of America suggest that 30% of children in foster care have severe emotional problems (3). Based on an inner-city study, newborns placed into foster care were 8 times more likely to be born to HIV-infected mothers than newborns who went home with their mothers (4). Two factors that may precede placement in the foster care system, sexual abuse and risky behaviors such as drug use or sexual activiy, also put young people at risk for acquiring HIV infection (5). In addition, the number of foster care children with handicaps and disabilities has been rising (6). As a direct consequence of many of these disorders, foster care children achieve lower educational levels and gain fewer vocational skills than children from AFDC families (7).

In a Washington State study comparing health care costs for children in foster care and for AFDC children of the same age, it was found that 25% of foster care children used mental health services vs. 5% of AFDC children (8). In addition, twice as many foster care children were hospitalized as were AFDC children. In terms of dollars, these statistics amount to $3,000 per year in health care expenditures for each foster care child vs. only $543 per child for children and their families who receive public assistance. Further analyses point to the fact that much of the health care used by foster care children is consumed by a small percentage (8%) who suffer from severe mental and neuro-

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logical disorders, including post-traumatic stress syndrome, cerebral palsy, hydrocephalus, and seizure disorders. Thus, children residing in foster care homes have a higher degree of health care needs that require more intensive and comprehensive services.

Methods

Of the total number of foster care children in the United States, approximately 4% (21,476) live in New York City (9). The Children's Aid Society (CAS) of New York City is a large provider of foster care and adoption services, which is independent of governmental services agencies. CAS developed the Medical Foster Care Program in response to the growing number of boarder babies (children with medical conditions abandoned at hospitals), and the Therapeutic Foster Care Program for children with mental health problems.

Data on 110 children entering CAS foster care were collected to analyze the health conditions affecting this population and the intensive service programs developed by the CAS to improve health outcomes. Each child in the study received a comprehensive medical assessment and history. As health records of foster care children are usually poorly maintained, additional information was gathered by talking with caseworkers at other agencies and with physicians. Medical findings, including data collected at follow-up medical visits, were corroborated throughout the six-month period. Age at time of placement was recorded as well as stated reasons for placement. The original 110 children in the study and an additional 26 received psychiatric evaluations.

Results

The CAS Medical Foster Boarding Home Program

Recognizing the high incidence of neglect, physical abuse and parental drug or alcohol abuse among foster care children in New York City, CAS started the Medical Foster Care (MFC) Program in 1988. The program currently serves 145 children, nearly 50% of whom are younger than 5 years old and 61% of whom are male. All of the children are considered medically fragile, as evidenced by congenital diseases such as heart disease, renal agenesis, cerebral palsy, seizure disorders and mental retardation. Many of the children in the program spent the first several months to years of their lives as "boarder babies" in hospitals, where they had been abandoned at birth.

The eligibility requirements for children in the MFC Program are listed in Table 1. The program's success stems almost entirely from the willingness of foster parents to step forward to care for these children. While medical foster parents receive stipends nearly three times higher than do regular foster parents, the requirements of their time and energy as caregivers suggest that their primary motivations are not monetary (Table 2).

The training of medical foster care parents consists of two parts. During the first or more traditional part, the CAS "home-finders" discuss issues such as prevention of child abuse, alternative methods of discipline, human development, emergency situations, separation, burn-out prevention, nutrition, safety, first aid, and common childhood illnesses. The second part is devoted to the unique medical caregiving that will be required of a foster parent based on a particular child's conditions. Once the foster parents complete this training and officially agree to accept a medical foster child, more intensive training enables them to be certified by

TABLE 1
Eligibility Requirements for Children in CAS Medical Foster Care Program

Criteria

- Child must be hospitalized or require high level medical facility;
- Child does not require lifetime institutional care;
- Child possesses a chronic condition sufficiently severe that it requires specialized attention, though not so specialized that medical foster care could not handle it safely.

CAS = Children's Aid Society

TABLE 2
Eligibility Requirements of Adults Seeking to Be Foster Parents in CAS Medical Foster Care Program

Criteria

- Participate in all orientation and training;
- Complete home study evaluation;
- Successfully complete a background check;
- Have physical examination;
- Identify one parent to stay at home;
- Appoint a back-up person (respite provider) for emergency situations

CAS = Children's Aid Society

a team of trainers that includes nurses and, if necessary, hospital staff.

The medical foster care child is placed with certified foster parents and is assigned both a CAS nurse and a social worker. The assigned nurse provides routine medical case management and advice for both the foster parents and the child throughout the period of care. In addition, the nurse helps parents arrange for specialty services and often serves as medical liaison, on behalf of the family, to health care providers. The nurse may also play a role as an informant for and trainer of the child's natural parent(s) should eventual reunification be possible. The social worker visits the foster home regularly in accordance with federal and state requirements. Once there, the social worker provides an assessment, counseling and support for the foster parents. Between visits, the social worker is also available for questions and advice, and can arrange for therapy and special care for the children. An important additional role for the social worker is making arrangements to provide for respite care, as well as assistance in maintaining the bonds and protocols between the foster parents, the child, and the natural parent(s) if reunification is still a possibility.

The CAS Therapeutic Foster Care Program

The Therapeutic Foster Care (TFC) program was started in 1990 to address the population of mostly older foster care children with severe levels of emotional and behavioral symptomatology. Nearly 80% of the 50 children in the program are between the ages of 5 and 11 years, with the other 20% between 12 and 18 years of age. Even compared with children in regular foster care, the conditions experienced by TFC children are more severe (Table 3), and consequently, TFC children experience a greater incidence of psychiatric disorders (Table 4).

Eligibility for TFC is restricted to those "who require individual intensive treatment but have the potential to function within a family unit in the community" (10). Most of the children referred to the program are either in a mental health facility or psychiatric hospital, or have had problems in several foster homes. The program provides traditional foster care services as well as services that are provided to children admitted into institutions and group facilities. It is based on the concept that children with severe emotional problems are likely to receive more stability through well-trained foster care parents than through a continuous path of institutionalization or relocation (as is often the case in other foster care agencies).

TABLE 3

Most Common Conditions Leading to CAS Therapeutic Foster Care and Regular Foster Care

	Therapeutic %	Regular %
Parental		
drug abuse	94%	45%
alcohol abuse	14%	14%
mental problems	44%	10%
Abuse		
neglect	50%	28%
physical	58%	23%
sexual	22%	7%

CAS = Children's Aid Society

TABLE 4

Psychiatric Diagnoses of CAS Therapeutic Foster Care Children and Regular Foster Care Children

Diagnosis	Therapeutic %	Regular %
Depression	42%	14%
Anxiety disorder	28%	19%
Adjustment disorder	20%	14%
Attention deficit/ oppositional disorder	64%	25%
Learning disability	20%	42%
Mental retardation	8%	19%
Psychosis	14%	0%

CAS = Children's Aid Society

As with the Medical Foster Care Program, prospective TFC parents must be married and have a designated respite care provider. The Children's Aid Society trains TFC parents through an intensive "basic" foster care training followed by 28 additional hours of therapeutic approaches to care. Parents are then briefed as to the specific condition of the child with whom they will be matched.

The TFC parent is assisted by a team of providers that includes a social worker, a sociotherapist, an art therapist and a psychiatrist. The social worker coordinates all the components of the program and arranges for the child's education, therapy and tutoring, as well as ongoing evaluation with the foster parents. The social worker also visits the home regularly and is the main contact with the child's biological parent(s). The sociotherapist trains, supervises, and supports the foster parents on specific methodologies considered essential to the child's long-term recovery and functioning.

Methodologies include active listening, communication, negotiation and motivation. The sociotherapist also serves as an advisor to the foster parents. Based on the mental diagnoses of the psychiatric clinic from which the child is transferred, the psychiatrist and art therapist are responsible for the development and evaluation of medication and art therapy treatments. Art therapy is primarily used for children with weak verbal skills. The psychiatrist uses play therapy and/or verbal therapy for ongoing diagnostic and evaluative purposes.

The Therapeutic Foster Care Program has been successful in its primary goal, providing its target children an opportunity to recover in the warmth of a home atmosphere as opposed to that of an institution. Its successes are apparent, in that a greater percentage of children are recovering in TFC than in institutional care. However, the program is not always successful. Some TFC children have been returned to institutions; others have advanced in only very slight degrees toward emotional stability.

Discussion

These data provide a description of the needs of some children in the care of the Children's Aid Society. As is indicated by the extensive services offered, these children need specialized treatment. The issue before the government and the public is whether to pay for this treatment now or face the consequences and costs of having a dysfunctional and dependent adult population later on.

In addition, health care providers need to stay informed on the overall subject of foster care. Their voices will be crucial in ensuring that the needs of these children are adequately represented to government, medical and other service providers. Criticisms leveled at the foster care system could compromise the well-being of the approximately 588,000 children who are dependent on it nationally (11). Health care providers can play an essential role in ensuring that this does not happen.

Finally, the systems of information maintenance and exchange surrounding the health care of foster children need to be improved. Despite information technology, some foster agencies are ill equipped to do adequate background checks on the youths involved and often deliver them to foster situations in which their major disorders either remain hidden or continue to go untreated. An adequately secured foster-link web page for agencies would help them document information and coordinate treatment plans more thoroughly and efficiently.

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Obtaining a History of Sexual Victimization from Adolescent Females Seeking Routine Health Care

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Abstract

Objective: To evaluate the clinical practice of direct physician inquiry of adolescent females during routine history taking and medical examination, with regard to their experience of childhood sexual abuse and/or assault.

Method: During a one-year period, a female physician directly questioned 146 consecutive female patients, aged 12–22, who were being seen for routine medical histories and physical examinations, as to whether they had ever been sexually victimized. Patients who disclosed histories of sexual victimization were immediately counseled and provided with appropriate on-site mental health referrals. Follow-up of these referrals was conducted to determine if patients complied with referrals to seek mental health services.

Results: For 141 of the 146 patients, the physician was unaware of a history of sexual victimization. Of these 141 patients, thirty-two (23%) cases were identified using this clinical strategy. Almost all (93%) of these young women accepted referrals for on-site psychotherapy, and 81% kept their initial appointments for psychotherapy.

Conclusions: The routine medical history and physical examination may be an appropriate setting for health care providers to accurately and comfortably elicit a history of sexual victimization from adolescent females, and provide appropriate referrals for mental health counseling.

Key Words: Adolescent health, ethics, sexual victimization, sexual abuse.

SEXUAL ABUSE RATES are alarmingly high for both boys and girls (1). Nearly 1 million children in the U.S. were substantiated as victims of child abuse in 1997 (2). The true incidence and prevalence of sexual and physical abuse are probably higher, as these experiences often go undetected and unreported (3).

In order to diagnose and treat adolescents who have experienced sexual abuse or assault, their trauma or abuse must first be disclosed. However, abuse victims often do not report their experiences (3). It is believed that direct questioning about physical and sexual victimization during routine medical examinations can effectively "interrupt the secrecy phase" that might otherwise keep the abuse hidden (4). But to accomplish this, primary care physicians, psychiatrists, and other health professionals must find ways to routinely elicit sexual victimization histories, or else many cases of abuse will continue to go unidentified and untreated (5, 6). The purpose of this study is to report on the clinical practice of direct physician inquiry of adolescent females who presented for a routine medical examination in a primary care setting.

Method

Direct physician inquiry was conducted with 146 consecutive adolescent female patients who presented for a routine medical examination at a comprehensive adolescent health care center during a one-year period. The patients involved in the clinical practice ranged in age from 12–22 years (mean age 16 years) and were all from inner-city neighborhoods from different sections of New York City. Patients'

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self-reported ethnicity was 58% Latino, 39% African-American and 3% Caucasian, which was consistent with the ethnic population seen by the physician doing the inquiry. At the time of this study, the physician had prior knowledge that 5 of the 146 patients had a history of sexual abuse (they had been referred to her with such a history), but did not have any parallel information on the other 141 adolescents.

Prior to taking each patient's history, the physician discussed confidentiality laws with the patient, making it clear that a physician is mandated to report any sexual abuse if it is disclosed while conducting the history. The physician then began with a series of questions that elicited the patient's health attitudes, behaviors and practices, and ended the session with the following questions: (a) Has anyone ever touched your body when you did not want them to? (b) Did anyone touch your breasts? Your vagina? Your buttocks? Anus? Or any other part of your body when you did not want them to? (c) Did anyone ever make you touch their body when you didn't want to? Where? and (d) If yes, was it your father? Your stepfather? Your brother? Uncle? Mother? Stepmother? Sister? Aunt? Grandparent? Teacher? Neighbor? Babysitter? Friend? Family friend? Stranger? Or any other person?

The physician used simple, straightforward language for all the questions pertaining to sexual abuse, in order to avoid confusion for the patients. These questions were all based on the physician's two decades of experience in working with adolescents. The physician also rehearsed the questions with a colleague prior to asking patients, so as to assure that the tone and demeanor did not fluctuate.

If, during the course of the questioning, the patient revealed a history of sexual victimization, her experiences and feelings were elicited and recorded. The physician then explored a number of issues with the patient, including the age of onset, the nature of the abuse (e.g., Did penetration occur? How long did the abuse continue? When was the last time she was abused?) and the relationship of the abuser to the victim. The physician provided support and clarified any misconceptions concerning the abuse. For example, it was often necessary for the physician to correct the belief held by many victims that they were the only ones with these experiences and that they were somehow to blame.

Again, using simple and direct language, the physician repeated her legal obligations to report the abuse to Child Protective Services and informed the patients of additional services that were available to help them work through the sexual victimization experience (including psychotherapy). Referrals were then made for individual, family, or group psychotherapy (or a combination thereof), according to the patient's needs. These mental health services were available on site, so that many of the patients could be directly introduced to mental health professionals, thus further facilitating their transition to appropriate counseling.

Results

Of the 141 female adolescents for whom no history of sexual victimization was known at the time of the routine medical history and physical examination, 32 (23%) disclosed a history of sexual abuse (Table 1). Vaginal penetration occurred in 63% of the overall cases, none within the prior 72 hours. Reported perpetrators included fathers, stepfathers, brothers, uncles, cousins, family friends, neighbors, friends, sexual partners and strangers. Through direct questioning, the physician found that of the patients who disclosed abuse and were given referrals, five were already undergoing psychotherapy (for reasons other than abuse-linked trauma) but none of these five victims had revealed their history of sexual abuse to their therapists. Of the remaining 27 patients, 25 accepted referrals and two refused, saying that they were "fine" and did not need or want to talk about the abuse (Table 2). Follow-up by the physician revealed that 20 of the 25 patients who accepted referral for mental health treatment kept their initial appointments for psychotherapy at the Adolescent Health Center Mental Health Program.

Discussion

Given the premise that it is advisable to question an adolescent patient on sexual victimization, three conclusions are suggested from the findings of this clinical practice: (a) Adolescent girls are willing to reveal a history of sex-

TABLE 1

Female Adolescent Patients Disclosing History of Childhood Sexual Victimization During Patient Interview

	N	%
None	109	77
Sexual victimization	32	23
Total	141	100

TABLE 2

Acceptance Rate for Psychotherapy Referrals of Adolescents with a History of Sexual Victimization Not Already in Psychotherapy*

	N	%
Refused	2	7
Accepted	25	93
Total	27	100

* Five of the 32 adolescents with a history of sexual victimization were already in psychotherapy but had not disclosed their history of abuse to their therapists.

ual victimization if asked directly by their health care provider in a confidential primary care setting; (b) The health care setting in which the questioning takes place contributes to the atmosphere of trust and safety that appears to be a prerequisite of disclosure; and (c) A majority of adolescent girls who disclose episodes of sexual victimization in the health care setting will probably be compliant with referrals for on-site mental health programs.

These data also point to the importance of using direct inquiry regarding the occurrence of sexual victimization when taking a history from adolescents. The observation that five of the patients in this study were already in psychotherapy but had not revealed their sexual abuse to their psychotherapists further emphasizes the need for direct questioning by providers.

The patients' reactions upon initial exposure to direct questioning varied considerably. For example, a 16-year-old teenage mother giggled upon hearing the first question, but when the physician explored the subject further, the patient disclosed a history of sexual victimization. She went on to describe how her own mother believed the perpetrator's allegation that the blood around her vagina was the result of her getting hurt during play. She laughed out of nervousness, because she had never even been given an opportunity to discuss the abuse in the many years since it had first occurred. This supports the view that how a patient reacts to the question has no bearing on the validity of her disclosure (or lack thereof) (7).

The use of a series of concrete questions, rather than a single question (e.g., "Have you ever been sexually abused?") is critical. In our experience, an adolescent may say no when asked if she has experienced sexual abuse, yet when asked what sexual abuse means, she will shrug her shoulders and admit she is not sure. When the concept of sexual abuse is clarified with additional concrete questions (e.g., "Has anyone ever touched private parts of your body without your permission?"), the patient may indeed reveal sexual abuse. In this type of interaction, a young woman may learn for the first time that what she experienced is considered inappropriate and abusive, and she may be empowered to seek services.

If a positive history is obtained, the provider could then inquire about symptoms of depression, suicidality, self-mutilation, or post-traumatic stress disorder. Such symptoms are common in survivors of abuse. The provider could also screen for symptoms of depression and post-traumatic stress disorder to ensure the patient's safety from self-injurious behavior. If the provider does elicit symptoms, the patient should be assured that these symptoms are common in teenagers who have experienced abuse, and that they might improve after she avails herself of mental health services.

There are several reasons why a routine medical history and physical examination may be an effective setting for inquiring about sexual victimization. The health care provider may be one of the few available confidants for a young person. The medical setting may also provide an environment where the subject of sexual victimization can be broached with younger patients in a less threatening manner. If this is the case, then health care providers must be better trained to elicit abuse history, react to disclosure in a professional yet compassionate manner, and ensure that their patients seek the appropriate follow-up. The health care provider also must be prepared to answer questions the patient may have, dispel some of the commonly held myths about sexual victimization, and replace them with realistic appraisals of the situation.

To what extent disclosure in this comprehensive primary care setting increases the likelihood of young victims accepting and following through on mental health referrals deserves further study. One factor that may have contributed to high follow-up rates in this study is the presence of an extensive in-house mental health services at the health center where the study took place. Medical providers who do not have these on-site resources should have a referral network that includes adolescent mental health service providers. In this situation, when other relevant adults are not available to accompany the adolescent, an outreach worker or other staff member could be assigned to accompany her to her first referral, to ensure compliance and address any fear or embarrassment.

Summary

While the primary care setting does not present the only opportunity for disclosure of sexual abuse, it has certain advantages. Health care providers, including nurses, physician assistants, physicians, social workers, psychologists, health educators and others, can provide an atmosphere of trust and confidentiality, take accurate histories, provide an environment where patients can feel comfortable sharing sensitive personal information, and make appropriate referrals. In doing these things, they can identify problems and facilitate treatment for many adolescent female victims of sexual abuse who might otherwise enter adulthood with unresolved issues related to that abuse.

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Where The Wild Things Are:

The Power and Challenge of Adolescent Group Work

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Abstract

Because groups are an intrinsic part of the adolescent's life, group therapy can be a powerful and effective treatment modality for them. However, it poses many challenges to group leaders and members alike. This paper, drawing on Maurice Sendak's well-known and beloved picture book *Where the Wild Things Are*, describes some of the issues involved in setting up groups for adolescents as well as how various developmental tasks of this age group appear in the group process. Clinical examples are utilized to illustrate the challenges and therapeutic efficacy of such groups.

Key Words: Adolescents, group therapy.

THE ADOLESCENT PEER GROUP serves a crucial role in the developmental tasks of this age group. Such tasks include: formation of identity, promotion and enhancement of self-esteem, incorporation of bodily changes into one's self-image, the development of intimacy, and separation from the family. The peer group also offers a refuge—there is safety in numbers. The universalizing aspect of the group—"we are all going through this together"—can be quite comforting. This natural propensity for group affiliation, together with adolescents' strong need to detach from the adults around them, makes group therapy a practical and sensible treatment modality for this age group. This paper describes the manifestation of these and other issues, utilizing a popular picture book to illustrate the themes of adolescent group work.

Max, the protagonist of Maurice Sendak's (1) classic picture book *Where the Wild Things Are*, is drawn to look like a child. Yet in many respects he behaves like the quintessential adolescent. He is oppositional and aggressive, indulges in regressive fantasy, adopts various identities, joins a peer group of like-minded individuals, and eventually comes to some resolution regarding issues of autonomy and independence. So, with apologies and gratitude to Maurice Sendak and Ellen Handler Spitz, a psychoanalytic art historian whose work (along with that of writers on both group and adolescent development) I will draw upon, I would like to examine Max and his cohorts through the lens of issues that arise during adolescent group work, together with their implications for treatment utilizing this modality.

For those readers unfamiliar with the story, I will summarize the plot. Max, while dressed up in a wolf suit, is mischievous and oppositional at home. His mother, whom incidentally we never see—her invisibility signifying her representation as archetypal "caretaker"—angrily calls him "wild thing." Max, furious, vows to "eat her up." She, in turn, sends him to his room without dinner. While in his room, Max envisions a forest and then an ocean, upon which he pilots his own private boat to a land where he meets large creatures (called "wild things") who are simultaneously threatening and humorous. They crown him king, and the group engages in a wild party, or "rumpus." Max then orders them to stop and sends the wild things to bed without their supper. An aroma of delicious food suddenly reminds Max that he is lonely for home, and he relinquishes

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his kingship, sails back home, back to his bedroom, where his supper is waiting for him, still hot.

The story opens with Max wearing a wolf suit, engaging in acts of aggression. He is defiant of the rules—he stands impudently on a book while destroying property (hammering a nail in the wall) and engages in an act of potential aggression (chasing the dog with a fork). I would suggest that Max's wolf suit represents his attempt at trial identification, an endeavor that many writers on adolescence such as Blos (2), Sullivan (3), and Erikson (4) discuss. Let me add parenthetically that for many years I had a poster of "Max and the Wild Things" hanging in my office, and I never ceased to be amazed by the response to it: nearly everyone who came into my office commented on it, from staff to child and adolescent patients—a population that cut across several cultures and ethnicities. I mention this because I think it speaks to the universal power of identification with aspects of this story. Max is, in essence, trying on a new identity in an effort to make it his own and integrate aspects of the "wolf" into his self-representation. The trial identifications in the story, as represented by the wolf suit, include aspects of identity from all developmental levels. Note that the wolf suit also looks suspiciously like pajamas, suggesting regressive, childlike tendencies. Note also the oral themes suggested by the notion of a wolf, as in Little Red Riding Hood, as well as Max's retort "I'll eat you up." And finally, one could argue, as Ellen Spitz does in her brilliant exposition of the story (5), that the pointed ears, extended claws and long tail may represent phallic appendages, suggesting the advent of sexuality—a theme quite relevant to adolescent group work. Spitz also perceptively notes the "wolflike" self-portrait of Max hanging in the hallway, which further gives credence to this notion of trial identifications and identity, including aspects of sexual identity. Spitz writes, "On the wall hangs a drawing by, and by implication a self-representation of, Max as an oral sadistic monster, bi-sexual, with plenty of teeth and hair (including a beard), eyes [that look] like breasts and a horn as a displaced phallus" (5).

These various aspects and levels of identity speak to the fluidity of developmental levels exhibited by adolescents, which can make the transference-countertransference matrix in adolescent groups quite a challenge. Thus, in one group, the group may engage in some abstract formal operational (to use one of Piaget's terms) discussion of moral principles, and in the very same session become regressed, rowdy, disorganized, and difficult to manage when discussing sex, while at the same time indignantly informing the group leader that the choice of food for snack leaves much to be desired. One day, a group at our center artfully arranged the food in sexually explicit imagery, in a manner designed to provoke the group leaders. A group therapist may thus alternately feel rewarded and gratified by the level of discussion, and frustrated and helpless at the rowdy, regressive behavior around him.

On the other hand, Yalom (6) and Sullivan (3), among others, have discussed how these trial identifications can be used for therapeutic gain in groups, as members begin to define who they are and who they are not, in contrast, similarity and opposition to the other group members and the leaders. Max's actions also represent behaviors characteristic of the early stages of adolescent groups. Most writers on adolescent group work describe the issues of power and control in the initial phases of group therapy, as members and therapists struggle to establish limits, boundaries, social hierarchy. This jostling of members may lead to transferential enactments of defiance of authority, challenging the limits, as well as steps toward destroying the fabric of the group (or even what may feel to the therapists as attempts to destroy them). For example, two of our therapists at the Adolescent Health Center began a group for adolescent young men struggling with issues of acceptance of sexual identity by themselves and others. One group member, C., who was an accomplished musician, a good student, and very articulate, showed up at the second group meeting noticeably intoxicated, a state that he proudly and defiantly announced to the group, a behavior which appeared to be a clear challenge to the group leaders and group. The group leaders, like Max's mother, felt that it was necessary to set a clear limit regarding this behavior. In the story, Max's mother calls him a "wild thing" in her attempt to contain his aggression. He retaliates, like many adolescents, with further aggression, threatening to "eat her up." In the adolescent group, C. did not take the limit setting around his substance use well. He became angry, threatened not to return to group, and on the weekend following the group meeting, hosted an "orgy" for the other group members at his home, in clear defiance of the group leaders/transferential figures.

People often ask which characteristics are necessary for an adolescent group therapist. In addition to a very healthy sense of humor, the ability to provide consistency, stability, and constancy in the face of provocation and aggression is critical. There is a recurring image throughout Sendak's book (and many other picture books, such as *Goodnight Moon*) (7)—that of the moon. Here, too, I quote Ellen Spitz: "Clearly, the moon figures in part as maternal symbol, not only because of its roundness, suggestive of the breast, but also perhaps because of its repetitive cycles: like the [caretaker], the moon disappears gradually and predictably reappears—changing shape but always recognizable. Illuminating the darkness, it again, like the [ideal] mother, serves as a beacon in the frightening realm [of the dark] unknown" (8). The appearance of the moon throughout Sendak's story suggests that regardless of the extent of Max's anger and aggression, his mother/caretaker will remain a constant presence in his life. This is something that August Aichhorn (9), a pioneer in adolescent group work, stressed as critical to group work with adolescents—the ability to contain aggression in a secure yet nonpunitive manner, while concurrently providing the reassurance that the group therapist will not be deterred (or destroyed) by the aggression. Winnicott (10), too, stresses the importance of constancy as well as the ability to withstand aggression as critical to providing a safe and nurturing environment for the infant, which in turn promotes development and differentiation of a cohesive self. Admittedly, this is no easy task, but one that is an ever-present challenge in adolescent group work.

Max, in the safety of his comfortable, secure, familiar bedroom, begins to imagine that the walls are falling away, and he enters a forest-like world with an ocean. Soon he becomes the captain of his own ship and sails away. Another critical task for the adolescent group therapist is to co-create together with the group a safe, secure space, not unlike Saul Scheidlinger's description of "the mother group" (11) or Winnicott's "holding environment" (10), in which issues, feelings, fantasies, hopes, and dreams can be explored. Within the secure confines of the group (not unlike the safety of Max's bedroom), as they enter the middle "working" phases of group development (12), members can begin to safely express difficult feelings. They can even regress, while also trying to learn how to "captain their own ships," that is, achieving some degree of separation and autonomy. Max is able to do just this in the secure confines of his room. In a group for HIV-positive adolescents, this might entail creating a safe enough space so that secret fears of mortality or rage at partners or parents who may have infected them can be shared; or in a group for rape survivors, allowing an adolescent girl to elaborate her revenge fantasies toward the man who had raped her, resulting in her not acting on such fantasies, and beginning to piece together and integrate the fragments of her horrific experience.

After his journey, Max comes face to face with the "wild things," who in many ways represent a peer group for him. The adolescent peer group serves a critical role in development—it promotes social/interpersonal learning, can help with self-esteem enhancement, and as writers such as John Meeks (12) and Peter Blos (2) point out, fills the vacuum created as the adolescent pulls away from his/her family of origin. A study of any junior or senior high school shows that adolescents find safety in numbers and that this developmentally syntonic propensity for group affiliation can make group therapy a truly powerful modality for this age group.

The wild things are tamed when Max stares into their eyes without blinking, and they ultimately cede leadership to him. In most adolescent groups, there will be challenges to the therapist (hopefully not in the form of wild things), perhaps in the form of provocative questions about the therapist's personal life, or challenges to the therapist's authority. Thus, the group may besiege the therapist with questions about the therapist's sex life, or threaten to destroy objects in the group room. Max's confrontation with the wild things can teach us that aggression must be confronted, unblinkingly so to speak. This serves to reassure the adolescent group that the leader is not intimidated by the group's aggression and can and will confront it, in the form of verbal intervention and limit setting. It also means that the group leader works hard not to personalize the provocations, but rather sees them as transference manifestations. Adolescents are curious, seeking identificatory figures. Their questions and interrogations of the group leader may serve multiple purposes: to throw off the leader, to provide the leader with the experience the adolescents themselves may have of feeling off-balance in the world, to defy the leader's authority and in this way enact their efforts at separation, as well as to discover just who this adult is who is running their group.

Max's taming of and acceptance by the wild things also serves to link Max with the creatures, suggesting yet another critical factor in successful adolescent group work—cohesion and the fostering of universality. The adolescent group therapist may not need "magic" to do this. Rather than staring into anyone's eyes, simple questions and comments that serve to create bonds and highlight commonalities among members can be just as useful. Universality, one of Yalom's (6) therapeutic factors for all groups, involves the understanding by all members that they are not alone, but share similar situations and predicaments. This can be a powerful tool in fostering a transference to the group and seeing the group as an agent of change. In one group I ran for adolescent girls whose parents were dying or had died of AIDS, the immediate commonality was obvious (14). Yet, these girls found other ways to develop cohesion and universality. From the start, they shared stories of visiting their parents in the hospital, and compared notes about whom they considered better caretakers—nurses, or doctors, residents and interns or attendings. The girls whose parents had died discussed the cemeteries in which their parents were buried. I was rather shocked by their candor, but kept quiet as I realized this was their way of connecting with each other. Ultimately, powerful bonds were forged between them, leading to a cohesive group.

Once cohesion is established, the group is free to "play" and explore issues. "Let the wild rumpus start," cries Max. And what does this wild rumpus entail? First and foremost, Max and his friends howl at the moon. Bearing in mind Spitz's (8) interpretation of the symbolic meaning of the moon, this has importance for adolescent groups, in particular for the transference toward the group leader. It signifies a challenging of authority (the moon as caretaker), which of course is crucial to adolescents' ability to develop a sense of who they are in relation to prevailing authority and which aspects of such figures they will choose to incorporate and which they will reject, as writers such as Blos (2), Anna Freud (15), and Erikson (4) note. So, you may think of yourself as the nicest, most understanding group leader on the face of the earth, but there's no guarantee that the members of your adolescent group won't use the opportunity to "howl" at you. Again, it is important to understand this as a manifestation of transference, not personalize it, and deal with it in a therapeutic manner. It seems significant that in Sendak's book we never see the mother—she remains off-stage, a transference figure whose actual physical appearance or characteristics are not as important as Max's reactions to her.

Then, Max and friends quite literally "hang," from the trees, that is. The relational aspect of the group is not to be underestimated, as Carol Gilligan (16) and others have shown us. Billie Corder (17), in her research on adolescent groups, found that adolescents rated the interpersonal learning aspect of group as highly therapeutic and beneficial. Adolescents use the group to learn how to function—with others and with themselves—and thus can learn to develop intimacy. In many of the groups we run at the Adolescent Health Center, we have found that the group members carry the group beyond the walls of the clinic. For example, in one group for adolescents who had lost a parent to HIV/AIDS, members began to meet at the subway and walk together to the clinic. Then, following the session, they waited for each other and walked as a group to the subway station. Now, there are those who forbid social contact by group members outside of group. But at the Adolescent Health Center, the group leaders and I felt this behavior was representative of the group's cohesion and that it signified the development of empathy, as some members waited behind for stragglers—both therapeutic gains. The relational aspect of group, together with the number of participants, also permits a multiplicity of identifications and transferences. Group members can "try on" different roles and identifications as they watch and observe all the group members, leaders included. Being the focus of such intense scrutiny and observation can understandably make some adolescent group therapists uncomfortable. Nevertheless, the mutuality and reciprocity inherent in such interactions is an important therapeutic aspect of group work, as adolescents and group leaders learn about themselves and from each other.

The last picture of the wild rumpus depicts Max riding one of the wild things. This may suggest that he has learned how to bridle his aggression, and perhaps how to use it effectively and adaptively. This picture is reminiscent of Freud's famous image (18, p. 18): "In its relation to the id [the ego] is like a man on horseback, who has to hold in check the superior strength of the horse.... the analogy may be carried a little further. Often, a rider, if he is not to be parted from his horse, is obliged to guide it where it wants to go...." Thus, the wild rumpus serves for Max as an arena in which he may experiment or play with his aggression, self-assertion, and independence and perhaps best determine how and in what ways he may use this potentially powerful resource. In fact, Billie Corder's research also indicates that adolescents value groups that teach them how to solve problems through role playing as well as how to learn positive and responsible methods of self-assertion. I would suggest that learning how to channel one's aggression and understand the consequences of one's behavior is an important goal for most members of adolescent groups and one that is hinted at in the picture.

Then, Max shows us his attempt at yet another identification. He orders the wild things to stop and sends them off to bed without their supper. Sounds suspiciously familiar, no? It seems to represent Max's attempt at identification with his mother who, earlier in the book, had sent him off to bed without his supper. The smell of "good things to eat" (from his home "far away") makes Max yearn for home. This, too, is suggestive of the adolescent's maddening push-pull, approach-avoidance stance toward adults. The very same Max who had wanted to sail millions of miles away from his family, now wants to return. In treatment, the adolescent group therapist must be prepared for the members' attempts to be simultaneously close to and separate from the therapist, a phenomenon most famously described by Peter Blos (2). In a group in an adolescent day treatment program, one group member (who was also in individual treatment with me) proceeded to sit next to me and place a paper towel on his head in an effort to both imitate me and mock me (and the yarmulke I wear), indicating a wish to both identify and connect with me, and anger me and drive me away with his provocation. Of course, how the therapist responds to such efforts toward separation-individuation as well as attachment will also determine aspects of the transference-countertransference relationship.

Max, in his decision to return home, relinquishes his kingship. If the adolescent group is to come to terms with their own limits, mortality, and identities, they must relinquish the narcissistic omnipotence and grandiosity that may characterize their interactions. According to Pumpian-Mindlin (19), the creativity and energy that accompanies the adolescent's grandiosity and sense of omnipotence needs to be harnessed and used constructively in the adolescent's life. It is important that the adolescent group retain access to the drive, intensity and passion that characterize this developmental period, while beginning to accept limitations, both external and internal. It is equally important that the adolescent group therapist enable them to do just that. Unfortunately, the energy, drive and sense of omnipotence of the adolescent group can pose a significant countertransferential challenge for the group leader. It is easy for the adult group leader to devalue or dismiss adolescent behavior as just that—"adolescent"—in part because it arouses in us unresolved feelings about our own adolescence and our own unresolved strivings for omnipotence. The fact is, adolescents are potent, vital and extremely physical, and their youth and exuberance can disturb the group leader, who must be careful not to fall into an enactment, dampening the group's enthusiasm, (much as a parent, teacher or other authority figure would). The adolescent group's zeal and energy, in other words, needs to be handled with respect.

Max takes leave of the group of wild things and they protest, "Oh, please don't go—we'll eat you up—we love you so," to which Max replies, "No!" Max, who was king of the wild things, co-conspirator of the wild rumpus, is now in danger of being eaten up by the same peers who cavorted with him a few pages earlier. This seems to be an illustration of the number and fluidity of roles in any given group, an aspect of groups that Fritz Redl (20) has described in great detail. A close examination of any group will uncover any number of roles taken on by group members, such as clown, monopolizer, leader's assistant, and scapegoat. Knowing who's who in a group can be an important source of information and help determine the leader's interventions, although there is no guarantee that the roles won't change, and quickly at that. Each group role usually reflects both the individual's and group's needs to enact that particular role. Thus, in one group of early adolescent boys, one group member was consistently regressed, disruptive, burping, farting, fidgeting, and interrupting others while they were speaking, and often running around the group room. The rest of the group seemed to organize around complaining about this boy's behavior and criticizing him for being so "immature and babyish." This boy clearly had individual predispositions toward behaving in an immature and regressed fashion and being picked on, thus receiving negative attention and recrimination, but it also served a purpose for the rest of the group—it allowed them to distance themselves from their own wishes to engage in regressive behavior and, in addition, gave them the morally superior hand. So the role served both individual and group needs, and had to be addressed on both levels.

Regarding scapegoating, Saul Scheidlinger described it in his classic article (11, p. 107) as "a group phenomenon as old as human history." It is a phenomenon that "entails simultaneous behavioral components from the individual-intrapsychic, the interpersonal, and the group-as-a-whole frames of reference." It is a defensive group maneuver, designed to help the group deal with unacceptable, and perhaps intolerable, feelings. Thus, in a group run for HIV-positive adolescents, S., a 17-year-old perinatally infected girl, was often ignored and her comments dismissed. In fact, partly due to her history of trauma and abandonment as well as her frail, diminutive physical appearance, she presented in a childlike fashion, and in this sense was quite different and "other" from some of the more streetwise, savvy adolescents who had been infected through sex. Also of note were her frequent hospitalizations and near-death encounter with pneumonia the previous year. What I believe the group had trouble dealing with was S.'s fragility and childlike, innocent demeanor, in addition to the precarious state of her health, which served as a constant reminder to the group of their own mortality and sense of "there but for the grace of God go I." S., then, had to be excluded, as the thoughts, feelings and fantasies stirred by her presence were too threatening to young people coping with a life-threatening illness. I should add that the group therapists, following Saul Scheidlinger's caveats, administered "psychological first-aid," that is, they intervened, and eventually the group members were able to discuss their own fears that were triggered by S.'s health and presence.

Perhaps Max is resisting being thrust into the role of scapegoat when he says "No." Rene Spitz (21) suggests that the exclamation "no" is an assertion of self and a step toward separation and the ability to define one's self, one's own wishes, desires, likes and dislikes, and express them clearly and forcefully to another. Max's experience in the group, as it were, allows him to decide what it is he wants and doesn't want. Then he begins the termination process, or final phase of group involvement, by stepping into his private boat and waving goodbye to the wild things.

The termination phase of adolescent therapy groups occurs when the adolescents, and their leader, begin to acknowledge that the group must come to an end. It is often characterized by sadness and mourning. Martha Wolfenstein (22), in her work on bereavement, describes adolescence itself as a trial period of mourning, as the adolescent must learn to relinquish his/her ties to childhood and parents; in essence, it is a loss of childhood and all that it entails. In this termination phase, the members may wax nostalgic over the events of the group. They may also regress, in an effort to recapture the early days of the group. But ultimately, they must be helped to separate and step into their own "private boats" to sail on with their lives. In the groups we run at the Adolescent Health Center, we try to mark each group's ending with some event or gesture signifying the ending. Thus, for one group for adolescents who had lost a parent to HIV/AIDS, the end of the year was marked by each adolescent designing and creating a panel that honored and commemorated the deceased family member for the national AIDS quilt. In a group for adolescent girls questioning their sexuality, the end of the group meant a special dinner celebration and a trip to a local gay and lesbian center where they could receive additional information and services, and establish linkages to the greater lesbian community.

Max travels back home, to his "very own room," where he finds his supper waiting for him, and Sendak ends the book with the telling phrase, "and it was still hot." In the final picture, once again, the moon (symbolic of the caretaker) is full and prominent. Despite all of Max's anger and provocation, his mother remains a constant, illuminating presence in his life. She shows Max that she can and will withstand his attacks, or as Winnicott lists as the final rule of treatment (19): "The analyst survives." The sight of the familiar, constant, reassuring moon as well as the hot food (with its implications of warmth and nurturance) make Max smile and, not insignificantly, he begins to remove the wolf suit. Among other things, this can suggest the importance of both the adolescent group leader and the group members themselves being able to survive the anxieties, the group process and the inevitable separation. As Ellen Spitz points out, "On the last page, there is no picture... [just the] words... 'and it was still hot'.... Love is ongoing and warm; it occurs in the intersubjective realm of language and consensual reality" (5, p. 445). But whatever lessons the child/adolescent learns from the story, in Spitz's words, "it probably takes a mother who is quite comfortable with her own wild things to be able to read this story again and again...." (5, p. 445). Perhaps that is an important lesson of the wild things for all of us leading adolescent groups. To create a safe enough space for adolescents to express themselves, take tentative steps toward separation and begin to develop their identity, we must be comfortable with the wild things in us. We must be able to tolerate and withstand aggression and sexuality as they appear in group; we must be able to playfully take part in a wild rumpus; and we must recognize and appreciate the exuberance and passion our adolescent patients are known for.

As for our patients, we must ensure that the adolescent group experience "remains hot." Hot, in the sense that we provide nurturance and support not unlike a warm meal. Hot, in the sense that we are unafraid to be in and put others in the "hot seat"—confront when it is necessary, keep the content and process alive and heated, and stay in the moment, as difficult as that may be at times. Ultimately, we hope that we can help our adolescent patients to emerge from the group experience, give up being "kings of the wild things" and use their experience in the play and fray to return to "the night of [their] very own room[s]" and proceed with the developmental tasks ahead.

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Legal and Ethical Issues Facing Adolescent Health Care Professionals

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Abstract

This article reviews the legal standards and ethical dilemmas surrounding the provision of care to adolescent patients. Uncertainty and ambiguity in this area has contributed to the underserving of the adolescent population. Usually, the legal right to consent to treatment resides with the adolescent's parent or legal guardian; however, there are many cases in which adolescents may provide their own consent. The determination that the adolescent is "mature" is one important factor. The law generally upholds a provider's determination of maturity of a patient. Minors also have the right to confidentiality in almost all situations in which they have the right to consent. The issue of confidentiality poses legal and ethical challenges to the provider in five discussed areas. Providers should be aware of the laws specific to their state, while keeping foremost the best interest of their patients. Providers should also encourage parental involvement and communication concerning treatment, while respecting adolescents' right to confidentiality.

Key Words: Adolescent health, ethics, legal issues, mandated reporting, patient confidentiality.

ADOLESCENTS AND YOUNG ADULTS are the most underserved age group in the health care system. Many physicians do not know how to apply the principle of confidentiality on behalf of their adolescent patients and may not know the types of services for which adolescents can provide their own consent. This article reviews the legal issues regarding adolescent health care and provides examples of ethical dilemmas that are commonly experienced by adolescent health care professionals. It also provides a series of recommendations to assist physicians and other health care professionals in making decisions that are legally and ethically sound. The provider must remember that the laws governing confidentiality for minors vary from state to state, and health care professionals must educate themselves as to the basic rights that are afforded to minors in their locale.

Consent Laws for Adolescents

Definition of Consent

Consent occurs when a patient voluntarily agrees to medical care with full understanding of his/her condition, the nature of the proposed treatment, alternative treatments, risks that may be associated with treatment, and the risk of no treatment at all (1).

Who May Consent to Care

For children, the right to consent to medical treatment usually resides with the parents, the legal guardian, or the foster care parent (2). If the parents are divorced or separated, the provider must not assume that both parents have the legal right to consent to care. In such cases, legal right depends on state law and court orders, especially in cases of joint custody. In these situations, it may be prudent to contact the court clerk for legal certainty. Under certain conditions, the right to consent for minors may rest with a designated proxy (2). For example, a parent may designate a proxy upon a child's enrollment in a school or summer camp, and the

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name of this designated proxy is placed in the child's medical record.

What about Adolescents?

Adolescents may consent to their own care if they are pregnant, parenting, married, or emancipated (1). An emancipated minor is one who is no longer in the custody of parents by order of a court, who is enrolled in the armed services, who is living independently, and/or who is economically independent of his/her parents. However, the determination that a minor is "mature" is the most widely used justification for reproductive health care services. Unfortunately, the definition of a "mature" minor varies from state to state (3). Typically, the provider makes an assessment when the teen independently presents for treatment. Although many states are ambiguous on the precise definition of a "mature" minor, the law has generally upheld the physician's assessment.

The legal system has recognized that most adolescents have the cognitive and mental capacity to make appropriate health care decisions; and they often do so under circumstances in which requiring parental permission might prevent them from seeking care or force them to take harmful risks (4, 5). The factors which should be considered in assessing a minor's maturity are chronological age, the risk, necessity and benefit of the proposed treatment, and the teenager's emotional and cognitive capacity for understanding treatment information (1).

Health Conditions in Which a Minor May Consent

A person under the age of 18, or a minor, may also consent to his/her own care in certain situations defined by state law. In most states, these situations include emergency health care, pregnancy-related care, testing and treatment for sexually transmitted disease (STD), drug/alcohol abuse services and some mental health care. In some states, family planning and abortion may also be provided with only the adolescent's consent. The following is a review of specific conditions and rules that govern a minor's right to consent to treatment:

Emergency care: In all states, any person in need of emergency care may be treated without consent if an attempt to secure consent would delay treatment and risk the patient's life or health (2).

STD treatment: In most states, minors can consent to their own care for all diseases that are reportable under the state's communicable and venereal diseases reporting laws (2). Moreover, if the presence of an STD suggests a possible instance of sexual abuse of a minor, the physician must report this finding to the appropriate child protection agency.

HIV testing: In most states, minors can consent to HIV testing. Due to the nature of the disease and the potential for discrimination, state laws respect the adolescent's right to make decisions which promote testing (1). Although HIV test results are confidential, state law requires disclosure of test results to certain individuals or institutions. Examples of these include health care personnel who care for the tested individual, mandated government health officers, third party payers, or an authorized foster care or adoption agency (6). However, an adolescent may choose to test anonymously, where his or her name is not given or recorded, and so may be able to maintain total confidentiality of the test results.

Family planning/reproductive health: The unfounded fear of many parents that contraception encourages sex has led to ambiguity as to the rights of minors with regard to reproductive health care services.

Currently, federal law upholds the rights of "mature" minors to receive reproductive health care (1). In no state is parental notification required for minors to purchase nonprescription contraceptives. In addition, no state explicitly prohibits minors from receiving prescription contraception (2). Certain states do, however, allow a physician to breach confidentiality and tell parents when he/she has prescribed contraception to their minor child. Some states also explicitly state the age (e.g., sixteen years) at which an adolescent may request drugs or devices that regulate contraception, but do not penalize physicians who treat patients at younger ages. Under federal law, adolescents also retain the right to receive reproductive health information. Federal law also explicitly states that minors on public assistance, Medicaid and Title X must be provided family planning services on request (1).

Prenatal care: Any minor in any state who is pregnant has the right to consent to prenatal care as well as labor and delivery services (7).

Abortion: Consent laws regarding abortion for minors vary widely from state to state. For example, Utah prohibits nearly all abortions, but the State of New York permits a minor to consent to abortion. Since 1976, the Supreme Court has expressed varied opinions on the rights of minors in this matter (7). In 1976, in *Planned Parenthood of Central Missouri v. Danforth*, the Court ruled that mandatory parental consent laws for teenagers were unconstitutional (8). In 1979, in *Bellotti v. Baird*, the Court ruled that a state could require parental consent if there was an alternative procedure in place for a minor to obtain authorization without parental consent (9). This procedure in most states involves a minor appearing in court to prove that she is mature and that an abortion is in her best interest. In 1990, in *Ohio v. Akron Center for Reproductive Health*, the Court upheld an Ohio law that mandated notification by the physician of parents or legal guardians of the intent to perform an abortion at least 24 hours prior to the procedure (10). However, minors can avoid parental notification if they receive official judicial authorization. And in *Hodgson v. Minnesota* (1990), the Court affirmed the view that court authorization was a viable alternative to parental notification for minors, but that it caused delay, harm and trauma for a young girl seeking to terminate her pregnancy (11).

Sterilization: Sterilization is against the law for all persons under the age of twenty-one (6).

Mental health services: Consent laws vary from state to state with regard to providing an adolescent with mental health services. Although a teenager may have consultation without parental consent, parental consent is usually required for mental health treatment. With regard to inpatient mental health services, some states have regulations that protect minors from being held longer than 72 hours without consent unless they are a threat to themselves or others, or a court petition mandates their involuntary confinement (1).

Alcohol/drug abuse: A minor is entitled to consent to confidential drug/alcohol treatment (2).

Immunizations: Although federal law clearly states that immunizations from communicable diseases are in the public interest and may therefore be administered to minors without parental consent, nearly all states have adopted legal exceptions due to pressure from religious and cultural constituencies (2). However, all states require that children attend school, and as a prerequisite for school attendance, children must be immunized for certain diseases. This requirement could be used by a teenager to obtain such immunizations regardless of parental consent.

Mandated Reporting

Child Abuse/Neglect Services

A physician must report any signs of child abuse or neglect to the appropriate child welfare agency. Health care personnel should provide immediate access to appropriate health services to minors who are victims.

Criminal Activity

Any manifestation of criminal activity involving a minor (e.g., gunshot or stabbing wounds) must be reported to a legal authority by the attending physician (2).

An Ethical Framework for Decision-Making

The Committee on Bioethics of the American Academy of Pediatrics concludes in their position paper (7) that “the physician’s responsibility to his/her child patient exists independently of parental desires and proxy consent.” The committee suggests that the role of the health care provider to “do no harm” for the patient remains a cornerstone of the physician-patient relationship. However, controversial topics such as abortion and reproductive health care often create doubt and hesitation. For example, some providers may not pursue a complete history, including sexual/physical abuse and substance use, in order to avoid dealing with the repercussions of consent and confidentiality laws, mandatory reporting and parental reaction.

Confidentiality and Minors

Definition of Confidentiality

Confidentiality is the principle that information cannot be disclosed without the permission of the person who consented to care (1). In nearly all situations in which minors have the right to consent to their own care, they also have the right to confidentiality. This precludes the provider, once they provide the service, from sharing any information with the patient’s parent, legal guardian or any other person not involved in the patient’s care without the explicit agreement of the teenager. However, confidentiality can and must be breached if the teenager is a threat to himself or herself or to the health of others, and in cases of abuse.

Issues Surrounding Patient Confidentiality

There are five significant areas in which the right to confidentiality poses legal and ethical challenges to the health care provider. These include (a) the nature of the patient-provider relationship; (b) patient concerns; (c) parental reactions; (d) payment for care; (e) the physician's values.

Unfortunately, adolescents have few sources to turn to for confidential and sound advice in making healthy behavioral decisions. Health care providers represent one of these sources, and their effectiveness in positively influencing their patients is directly related to the trust developed in the patient-provider relationship. Consequently, a provider must discuss issues of confidentiality with adolescent patients and their parents at the beginning of the first medical encounter. This conversation should include the protections and limits of confidentiality, and reinforce the understanding of patients every time a condition or behavior that seems to call for parental notification becomes evident. Violation of the patient-provider relationship through disclosure of health information to parents, legal guardians or others without informing the adolescent patient may cause the teenager to distrust both the particular provider and the health care system as a whole.

The provider must also weigh the individual concerns of the adolescent patient. Usually a teenager makes confidentiality an issue either overtly or covertly during a routine health screening and will not disclose certain behaviors until he/she learns that they will be kept confidential. For example, one teenager may ask if a parent or grandparent will be told of what transpires during the examination, while others wait for a cue from the provider that their discussions will be confidential before they respond to important queries about sexual behavior and alcohol/drug use.

A third factor affecting confidentiality is the parent's reactions. Despite the absence of parents in the examination room, the possibility of parental objections should be anticipated by providers whenever they provide treatment and consultation to adolescents, especially if that treatment involves reproductive health care. Handling such issues may be particularly difficult if the provider has had an ongoing relationship with the parent. However, with adequate preparation the provider can both provide confidential services that meet the adolescent's needs and help parents understand and support the provision of these confidential services. The key is to make this process and these conversations an integral part of the provider's health care delivery. Providers must explain to parents the reasons for confidentiality and include these conversations as patients move from childhood to adolescence. In addition, providers must encourage parents to keep communication open with their adolescent and to view confidential health care as a sign of responsibility and of learning how to become a good health care consumer.

The changes in health care financing pose an additional challenge to patient confidentiality. Numerous and complicated billing procedures by private insurance agencies often require that the health care provider disclose treatments in order to receive compensation (12). Because parents pay for most insurance plans, a bill can become the outlet where confidential information is breached. Physicians can attempt to minimize this by taking additional precautions to explore the billing procedure of a minor's insurance company or by providing services for a fee that the adolescent can afford, including free services when necessary. However, time and institutional pressures sometimes make these options prohibitive.

Finally, a physician's own values may affect his ability to provide care to a patient and maintain confidentiality. This is particularly the case for physicians who do not believe in the acceptability of certain behaviors or treatments and are therefore inclined to disclose information to parents, thinking it in the best interest of the adolescent's development. In this case, physicians must explain beforehand their philosophy in providing service and their ability or willingness to provide confidentiality.

Health care providers must address at least three areas of concern when they see adolescents. First, the provider must begin with what is clinically appropriate to do, given the physical, emotional, and mental health condition of the patient. Then, the provider must weigh the legal issues surrounding the proposed treatment, including the consent and confidentiality laws governing their actions in their particular state. Finally, the provider must consider other possible barriers to care for the patient. This is particularly important with adolescents who may not be able to travel to another facility or who cannot afford to pay their fees directly. In these cases, this provider may be the only person available for addressing a particular health issue or, if the provider cannot offer the needed services, he or she may need to counsel the patient on alternative options elsewhere.

Recommendations

Clearly, all health care professionals need to familiarize themselves with the rules that govern consent and confidentiality in their locale. Moreover, the health care provider should understand that in many situations a minor has the right to receive care even without parental involvement; and if New York State serves as an example, a physician has never been held liable for providing care to a minor whom he or she judged to be "mature" (1). The following additional recommendations are intended to help health care providers responsibly tackle the issues of consent and confidentiality, maintain the respect of patients who are minors, and work effectively with their parents.

- Always inquire into the feasibility of parental involvement when treating a minor and ask which other adults are important in their life, so that they might be involved in the care;
- Encourage open communication and parental involvement, whenever possible;
- Be aware of the laws in your state and respect the rights of the adolescent;
- Advocate for what you think is best for the adolescent.

Conclusion

Providing services to adolescents is not without its ethical struggles. Providers must continuously evaluate how treatment can be administered while at the same time respecting legal mandates and the implicit will of parents and guardians. While there are no easy solutions to the challenges of adolescent health care, there are clear and negative consequences to not acting in the interest of adolescents.

Providing health care for adolescents is a major opportunity to help them cope with the challenges in their lives, develop healthy behavior and become responsible health care consumers. A close relationship between adolescents and the people who can competently, affordably and confidentially render health care services helps adolescents become healthy, responsible adults.

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CHIP:

New Opportunities in Adolescent Health Care Delivery

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Abstract

Children's Health Insurance Programs (CHIP), usually targeted to infants, toddlers, and school-aged children, have been expanded to include adolescents. Adolescents need some form of health insurance in order to access needed care. Moreover, programs and services that provide them with health care must be adolescent-friendly, adolescent-focused and adolescent-sensitive, and include specialized training for primary care providers. Translating this philosophy into a successful health care delivery program involves addressing the psychological, institutional and financial barriers that make it difficult for adolescents to access health care. Overcoming these barriers, especially the financial ones, requires that primary care providers advocate for teenagers and take advantage of resources made available for them. CHIP provides a critical opportunity for policy-makers and health care providers to further improve adolescent health care and to more fully integrate adolescents into the health care system.

Key Words: Adolescent health. CHIP, health insurance, ethics.

The delivery of adolescent health care is at a pivotal stage because of the Children's Health Insurance Program (CHIP) mandate to provide access to adolescent health consumers. CHIP targets families who earn more than is permitted under traditional Medicaid programs—up to 200% of the federal poverty level—but do not have private insurance. It is estimated that CHIP will provide coverage for health care to 3 million previously uninsured children and will identify an additional 660,000 children who are eligible for Medicaid but currently are not enrolled (1). In order for practitioners to take advantage of this resource, implementation of CHIP programs needs to be incorporated into a larger adolescent health care strategy that addresses all the impediments which this population faces, financial and otherwise. Such a strategy must build upon a proactive philosophy toward adolescents as health care consumers and use this philosophy as an impetus for more adolescent-sensitive provider training, more flexible hours, "teen-friendlier" facilities, and outreach. This article will describe a proactive adolescent philosophy, examine three critical barriers to successful adolescent health care delivery, and then evaluate the potential impact of CHIP as a resource for advancing adolescent health care.

Developing a Proactive Adolescent Health Care Philosophy

Unfortunately, many teens facing health problems today do not receive any kind of care. Services for this population need to begin with the adoption of a proactive philosophy toward adolescents with respect to their health care. Many CHIP programs are already targeting young children, infants and toddlers, because these populations have been afforded greater attention both within the medical community and by society. However, adolescents must be treated as a separate age group that is unique and, therefore, not appropriately categorized as either children or adults.

Recognizing adolescents as a distinct group of health consumers necessitates appreciating

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their uniqueness. The physical, mental, emotional, cognitive, reproductive and social changes that they undergo are of a range and intensity that can be likened only to those of infancy. These almost sudden and simultaneous occurrences, often beginning at the end of the first decade of life, leave these young people with vital questions that impact upon their entire future—questions about themselves, their gender, their social identity and their personal values. Health care providers can have tremendous impact as positive role models and as sources of information, as adolescents and their families tackle these issues.

Tied into the period of adolescence is a normal desire to experiment that includes trying different hairstyles, different clothes and even different personalities. Unfortunately, this curiosity can also make these young people vulnerable to a host of behavioral and health disorders, such as alcohol and drug abuse, violence, early unintended pregnancy, sexually transmitted infections and suicide. Approximately one million adolescents in the U.S. become pregnant each year, 85% of these pregnancies unplanned (2, 3). In addition, three million adolescents per year acquire sexually transmitted diseases (4). While the incidence of gonorrhea and syphilis among teens has decreased steadily over the last two decades, contraction of HIV has increased (4). Nearly 25% of adolescents through the age of sixteen report having experienced assault or abuse during the previous year (5). Roughly six million teenagers (or 20%) report that they had been depressed during the previous two weeks, and between 1980 and 1992 the rate of suicide among adolescents increased by 120% (5).

While the vast majority of adolescents ultimately reach adulthood with healthy attitudes and positive life goals, all adolescents can benefit from a relationship with responsible adults, including medical providers who are sensitive to their individual challenges. A proactive philosophy of adolescent health should be based on awareness of the impact we as health care providers can have on easing the challenges associated with adolescence. Effective health interventions must be built around the reality that adolescents do want to live their lives free of violence, sexually transmitted infections, drugs, gangs, untreated illness, depression and suicide.

To increase the chances of adolescents living healthy lives, access to a health care system that works with them to enhance their resiliency and provides them with more comprehensive services than conventional medical treatment is required (5). Programs and services must be adolescent-friendly, adolescent-focused and adolescent-sensitive. Providers must be given opportunities to receive training that includes: communicating effectively with adolescents; asking developmentally appropriate questions; screening for multiple risks; and conveying accurate information regarding confidentiality and consent laws. They also must be allowed to spend more time with these patients in order to develop trusting relationships. Perhaps most important, adolescents themselves must be recognized as an age group that merits our attention apart from other age groups. A proactive adolescent philosophy is, quite simply, one that places value on adolescence.

Components of Adolescent-Sensitive Care

Translating this philosophy into components of a successful program involves recognizing the greatest barriers adolescents face to receiving health care. These barriers are psychological, institutional and financial.

Psychological Barriers

The greatest concern that adolescent patients face when visiting a health center is that “someone might find out [they] have a problem.”

There are several explanations for this concern. A majority of health problems that adolescents face have their origins in sociocultural and behavioral factors (6). Teenagers are often embarrassed and ashamed to undergo a pregnancy test or sexually transmitted disease screening, or receive mental health counseling for alcohol and drugs. These are all conditions that they do not want to advertise to their peers. Their shame is compounded by the peer pressures of adolescence, urging them to “fit in” and “be cool.” Visiting a health care provider creates a dilemma in that it places a teenager at risk of being ostracized for “doing things differently.”

As if social pressures were not enough, parents may compound a teen’s concerns. While parents are the most important influences in a teenager’s development, teenagers are at a maturity stage in which they are beginning to make their own decisions about their physical, social and reproductive activities. Adolescents must weigh many factors besides parents when making these decisions, including self, peers, teacher, religious representatives and even the media. Visiting a health care provider places teenagers at risk that their parents may discover their behavior or its consequences. For many teens this risk alone is enough for them to delay seeking preventive health information and/or forgo crucial care.

For health care providers, a proactive adolescent health care philosophy must echo one of the most basic tenets of the medical profession: the patient must come first. In the case of adolescents this means establishing, assuring and abiding by confidentiality rules. Providers should explain from the beginning that the doctor's office is a safe haven in which no information will be shared with parents, peers or any other outsiders. Providers should also explain the exceptions to these rules, e.g., cases in which the adolescent discloses child abuse or is a physical threat to himself/herself or to others. Providers should seek training on how to discuss the confines of confidentiality with their adolescent patients and they should stay informed as to any changes in confidentiality regulating requirements. Providers should also seek every opportunity to emphasize to adolescent patients the importance of sharing their health concerns with their parents and of making parents partners in their health maintenance and/or recovery.

Institutional Barriers

Another reason that patients give for not seeking services is that they simply do not know where to go. For teenagers who are just beginning to develop a sense of independence that sometimes puts them at odds with "adult" institutions, dealing with a large medical facility like a hospital may be perceived as too complex or frustrating.

Even if teenagers attempt to seek care from medical institutions, they may encounter a cold and unfriendly atmosphere and feel that adults do not welcome their presence. These perceptions have some validity, since health care providers work in a medical setting that has been designed by and for adult consumers. To attract teens, we need to reconsider the physical location, structure and atmosphere of the health facilities. This means establishing a separate building, entranceway or wing that only serves teens. Such an area can contain flyers, brochures, and wall hangings that specifically address teen health concerns. Receptionists and other staff can be trained to make teens feel comfortable from the moment their health care begins.

Related to this need to overcome institutional barriers, adolescent care facilities should also seek to develop comprehensive and interdisciplinary services so that teens can seek care for many of their needs under one roof. The Mount Sinai Adolescent Health Center accomplishes this "one-stop shopping" by housing primary care, mental health care, reproductive health and specialty services in one building. Patients who visit the center are seen by primary care providers, health educators and mental health professionals, when necessary, to ensure a comprehensive bio-psycho-sociocultural-spiritual response to a particular need. Also, adolescents seem to like the idea that one place is specifically designed for them.

For medical centers which cannot establish a wide range of in-house services, referral networks should be established with adolescent-friendly facilities or adolescent-friendly providers. Outreach workers or other staff should also be assigned to accompany teens on their first referrals, to ensure compliance and ease their anxieties.

Lastly, a teen-friendly facility should seek to accommodate teenagers at times convenient for them. For adolescents, this usually means after school, evenings and weekends. Outreach efforts should also be directed where teenagers congregate and should include peer outreach workers. Handouts should feature the image of adolescents, rather than adults or younger children, because adolescents often respond most positively to their own age group.

Financial Access

Teenagers, as a group, are the least likely age group to have health insurance (6). While one in five teenagers has a serious health problem, one in seven does not have health insurance (5, 7). One in three adolescents eligible for Medicaid is not enrolled, and private insurance for adolescents is becoming increasingly restrictive (5, 7). As a result, in the past two decades, the number of young people in private health plans who have lost coverage has exceeded the expansion of Medicaid, leaving this nation with the largest percentage of uninsured youths in its census-taking history (8). As of 1997, nearly 11 million young people lacked medical coverage (9). Even when they are insured through their parents' policies, they may fear accessing health care because they don't want their parents to know about the health care services they are obtaining. When the parents receive the explanation of benefits about the adolescent's visit from the insurance company, the confidentiality will be breached. The situation is further exacerbated for teens from poor communities. These youths are dependent on centers that will treat them for free or for minimal fees.

Overcoming financial barriers involves providers advocating for confidential billing procedures to health insurance companies, and subsidized funding (public and private grants) for those adolescents who cannot afford care, as offered by the Children's Health Insurance Program.

Taking Advantage of CHIP to Improve Adolescent Health

The Children's Health Insurance Program (CHIP) provides a critical opportunity for policy makers and health care providers to further improve adolescent health care and to more fully integrate adolescents into the health care system. There needs to be an intergenerational approach to health care and health care coverage, inasmuch as what affects one group will have an impact on others. Despite enacting Medicaid in 1965, it was not until 1998 that Congress approved extensive legislation to provide health insurance for children in need in America (1). The CHIP legislation authorized $24 billion over five years and $48 billion over ten years, for states to initiate and expand the provision of child health assistance to uninsured, low-income children. Of these funds, 10% were set aside for administration and outreach.

The specific framework for how CHIP funds are to be used is designed by individual states and then submitted to the Department of Health and Human Services (DHHS) for approval. Once a state's plan has been initially approved, future modifications of CHIP are left entirely up to that state. Consequently, training and advocacy on adolescent issues in CHIP plans will need to involve not only health care providers and plan administrators, but state legislators as well.

While financial and other resources available through CHIP can be instrumental in remedying the increasing lack of coverage for young people, guidelines set forth by the DHHS also enable CHIP plans to be used for: (a) developing outreach activities, (b) increasing enrollment, and (c) ensuring the quality and appropriateness of care (10). When applied to a proactive adolescent health care philosophy, these measures make CHIP an even more formidable piece of legislation for revolutionizing adolescent health services.

Health care providers should work with legislators to use media to launch a "teen-friendly" outreach campaign to promote teen health and health care enrollment among the 3 out of 4 persons under 18 who qualify for but are not currently receiving Medicaid. As mentioned above, advertising campaigns are needed that address teens' right to health care and provide them with the initial guidance for seeking it. Some of these campaign efforts could be tested at schools, recreation centers and other teen hangouts. They could be paid for by the 10% of CHIP funding earmarked for outreach and administration. Appropriate staff and youth advocates who conduct these campaigns should be trained in communicating with teenagers and in anticipating the types of concerns that they will have (e.g., confidentiality, filling out applications, finding the right provider, etc.). Legislators can facilitate these types of programs by making adolescent-specific outreach, training and demonstration projects a funding priority.

Providers should also use CHIP to expand outreach to special populations of youths who often have the least access to adequate and proper health care, coverage, and information. Included in this category would be adolescents in correctional facilities, teens in shelters, and "undocumented" youths. Since many of these special populations do not have advocates in the political system, their inclusion in CHIP would depend on the combined efforts of legislators and "safety net" service providers.

In every outreach effort, CHIP providers should be sensitive to the gender and culture of adolescents. Males may be more difficult to engage in health care because they may not understand the benefit of health programs until an emergency / crisis situation arises. On the other hand, females may be resistant to reproductive health care unless it guarantees them a safe and confidential setting. Attractive brochures should publicize the nature and benefits of the health care services being offered. In keeping with a proactive adolescent philosophy, outreach materials need to assure teenagers of their right to confidential services, and they should explicitly state the specific types of services to which adolescents can provide consent. Outreach brochures should also be multilingual, to address the growing number of non-English-speaking uninsured.

In terms of financial barriers to care, CHIP can have even greater impact if adolescents are permitted to self-enroll. Current stipulations provide temporary self-enrollment under the "presumptive eligibility" clause—through which a teenager may fill out an application for certain types of services (e.g., reproductive health), receive care, and seek parental involvement only after his or her eligibility is corroborated by the state. While presumptive eligibility is essential for guaranteeing immediate provision of care in many circumstances, it is insufficient as a mechanism for ensuring long-term adolescent involvement in the health care system. It would be more effective if parents were invited to participate in care by the teenagers themselves. This could be accomplished by permitting teen self-enrollment and training health care providers to counsel teens on the importance of parental involvement. This would help adolescents receive the services they need and, at the same time, increase the possibility of engaging parents.

The actual enrollment procedures for Medicaid and CHIP programs need to be as straightforward as possible, to avoid overwhelming or confusing the applicants. Simplification of enrollment forms also facilitates adolescents' access to services and helps to ease their initial anxieties about seeking care. Enrollment should take place in community settings such as health services sites, schools, recreation centers and other adolescent-friendly locales. In these settings, eligibility for health care programs could be linked to qualification for other subsidized programs, like school lunches, or even more simply, have all uninsured teens qualify.

A mechanism should also be developed to ensure that coverage is not lost because of sudden disqualification or a need to "switch" program coverage. This is particularly important because Medicaid and CHIP target families whose incomes are subject to considerable fluctuation. Enrollment needs to be guaranteed for a prescribed period of time (e.g., one year or more) regardless of family income fluctuation, with a seamless movement from one coverage program to another, or at least a system that will alert program administrators when loss of coverage is imminent.

Providers should also use CHIP as a basis for advocating for legislators and plan administrators to cover a wider range of health care services that are similar to those mandated by Medicaid. In some states, mental health and substance abuse services are not provided within their plans. In other states health education and counseling are not provided. Under some religion-based managed care plans, adolescents are unable to receive access to contraception and abortion. Adequate health care must be comprehensive and interdisciplinary to ensure health maintenance.

Conclusion

CHIP provides a significant window for improving the health of all people under the age of 19 years. Although CHIP initiatives continue to emphasize younger age groups, it is essential to target adolescents for enrollment, so as not to eliminate the chance of reaching their unmet health care needs. Over the next few years state policy makers and health care professionals should continue to design and redesign plans to actuate the goals of CHIP.

The recommendations presented here highlight the importance of legislators, insurance administrators and health care providers when considering a proactive adolescent health care philosophy in launching CHIP initiatives. When this philosophy is followed by steps to facilitate enrollment and enhance adolescent-appropriate services, CHIP resources can better overcome barriers to adolescent health care and change the landscape for adolescents as consumers in the health care industry. Perhaps health care can then become a truly intergenerational priority in these families, because the health care access of one member of the family will have an impact on the others.

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Adolescent School-Based Health Care:

A Description of Two Sites in Their 20th Year of Service

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Abstract

Purpose: While there are currently nearly 1,400 school-based health centers (SBHC) nationwide, only 20% have been in operation for more than 10 years. The Mount Sinai Adolescent SBHC Program is now in its 20th year of service. The purpose of this study is to: (a) present the demographic data for 2003 high school SBHC medical visits, including age, sex and insurance status; (b) describe the current prevalence of medical and psychosocial risk factors of the students seen for examination; and (c) present general distributions for psychosocial risk factors found in 1988 archival information and note differences from current risk factors.

Methods: A retrospective chart review was conducted in high school A, whose SBHC serves students mainly interested in going to college, and in high school B, whose SBHC has a heterogeneous population with a large proportion of recent immigrants. Data collected included demographic variables as well as reports of risk factors such as: considering oneself to be overweight, history of sexual activity, history of sexually transmitted diseases, same-sex attraction, use of alcohol, cigarette smoking, use of marijuana, suicidal ideation and exposure to violence.

Results: For those participating from high school A (n=231): 78% female, mean age 15.75; asthma (17%); think oneself overweight (30%); family member with HIV (11%); sexually active (35%); same-sex attraction (3%); cigarette use (14%); marijuana use (13%); alcohol use (38%); suicide ideation (14%); witnessed violence (37%); and overweight and obese (33%).

For those participating from high school B (n=241): 64% female; mean age 16; asthma (16%); think oneself overweight (32%); family member with HIV (9%); sexually active (43%); same-sex attraction (7%); cigarette use (38%); marijuana use (24%); alcohol use (53%); suicide ideation (23%); witnessed violence (33%); and overweight and obese (31%).

In 1988, students at these schools reported: sexually active status (41%); marijuana use (13%); cocaine use (12%); alcohol use (20%); and sadness/depression (43%).

Conclusions: While a snapshot of the risk factors in 2003 might indicate that sexual activity has decreased somewhat, substance use, as well as eating-related and AIDS-related issues have come to the forefront. SBHCs continue to serve students with intense medical and psychological needs. It remains crucial that SBHCs provide comprehensive medical and mental health services.

Key Words: School-based health, school health programs, adolescent health.

Background

THE FIRST SCHOOL-BASED health center (SBHC) was established in 1970 as a new model of health care for children and adolescents. There are now nearly 1,400 SBHCs nationwide (1). Adolescents are served in approximately half of these SBHCs. SBHC users are likely to be medically underserved and at risk for medical and psychosocial problems. Research suggests that high school SBHCs contribute significantly to improved access to medical specialty services for those teens who need them (2). High school SBHCs provide access to primary care, thereby enhancing efforts to provide primary and secondary services for the prevention of adolescent morbidities (3). This is especially important in light of the report by Blum et al. of inadequate teen health risk assessments in non-teen-focused sites (4).

Literature about high school SBHCs describes strong parent and student support and use (5, 6). Parental support of reproductive health services has been demonstrated in a community sampling study by Santelli et al. (5). In fact, 63% of parents endorsed a full range of clinic services; approximately 75% of the parents of sexually active teens supported providing birth control pills or condoms.

The greatest number of SBHCs are in New York State. Of the 181 sites, 70% are located in New York City; 33% are hospital sponsored and 20% are in high schools. Mount Sinai Medical Center oversees two New York City high school sites and four East Harlem elementary school sites; it is linked to four additional sites in Washington Heights through collaboration with the Children's Aid Society. This article will focus on our two high school programs, now in their 20th year of operation, describing the demographic, medical and psychosocial characteristics of SBHC users.

The Mount Sinai Medical Center was first to establish a high school SBHC in New York City. In 1983, the Adolescent Health Center of

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the Division of Adolescent Medicine, in conjunction with the New York Community Trust and Community School District #4 and the subsequent support of the New York State Department of Health, opened a school-based health center in high school A. In 1984, a second school-based health center was established in high school B. The Mount Sinai Medical Center's SBHCs have served as model programs for other organizations developing school-based programs in the metropolitan area.

The Mount Sinai high school SBHCs render care to adolescents and provide support to high school faculty and parents concerning students' medical and mental health needs. Utilization rates (for medical, reproductive health, mental health and health education services) in our high school SBHCs have increased over time, with more than 80,000 visits since the program's inception. Students have expressed their satisfaction with our services because of easy access and staff availability. Student satisfaction is evidenced by 85% of them giving the SBHC a grade of "A," as well as indicating that they "would recommend" the SBHC to a friend.

Over the last 20 years, in response to pressing medical and mental health needs, we have utilized New York State Department of Health (NYSDOH) and Medicaid revenue funding to increase the SBHC program's presence at high school A from part-time to full-time. (High school B has almost always had a full-time presence.) Both schools attract students from throughout New York City. Patients represent a wide range of socioeconomic, racial and ethnic backgrounds including the predominately low-income and working-class Latino and African-American communities of East Harlem, Central Harlem, Brooklyn and South Bronx. In 1994, high school B evolved from one large urban high school into five separate "mini" schools. This was done as a way to improve the educational process and to better meet the needs of students.

Methods

Facility Description

In addition to providing comprehensive primary medical, mental health, reproductive health and health education services, the high school SBHCs also respond to acute and episodic complaints, utilizing a multidisciplinary approach. Teams consisting of a nurse practitioner / physician assistant, clinical social worker, medical office assistant, health educator, school health worker and adolescent medicine physicians work closely with parents, faculty and community leaders to accomplish their goals. Students seen for a history and medical examination are asked to complete a database form that includes history of medical problems, surgery and immunizations as well as a mental health history for problems such as depression, sexual abuse and suicidal ideation. Students seen by one professional are frequently referred to another. As per Board of Education and NYSDOH requirements, all students enrolled must have parental consent. The SBHCs are an integral part of the Mount Sinai Division of Adolescent Medicine and as such are able to access physician coverage during evenings and weekends. Each team member participates in discipline-specific continuing educational sessions and receives clinical supervision and support within the Adolescent Health Center.

The high school SBHCs provide services to students from 8:30 am – 4:00 pm daily, with direct medical services at each site available 30–35 hours per week, mental health services 24 hours per week, individualized health education 14–16 hours per week and first aid 37.5 hours per week. The sites are located on the first floor near the gym and have one or two examination rooms, a confidential counseling room, a waiting room and laboratory space. The consent form allows the parent/guardian to choose specific services that can or cannot be provided to his/her teen. There are no out-of-pocket expenses by the student, but insurance and Medicaid information is requested. The high school SBHC charts are maintained separately from school health records. When the sites are closed for summer vacation, the medical records are transported to the Adolescent Health Center of the Division of Adolescent Medicine and are available for student visits there.

Nationally, nearly all SBHCs offer treatment for minor acute illness (96%) and comprehensive health assessments (90%). Psychosocial assessments are offered by 80%, while 67% offer brief therapy for mental health problems. Only 56% of secondary school centers provide gynecological examinations and 60% provide diagnosis and treatment of sexually transmitted infections (1). The Mount Sinai Adolescent SBHC sites demonstrate the accessibility, breadth of clinical service and support of educational goals that make the comprehensive SBHC model a significant component of health service delivery for teens.

Data Reviewed

Information collected was obtained during visits in the 2002–2003 academic year. Data was obtained for demographics, including insurance status and general distributions for medical and psychosocial risk factors, in 472 comprehensive health evaluations. The program's enrollment consent form includes provision for review of medical charts for program evaluation. A specifically targeted classroom health education program was developed upon review of these students' risk factors. Additionally, in response to the high prevalence of students who are overweight and obese, an after-school fitness program was developed.

Results

Enrollment and SBHC Users by Age and Sex

The 2,090 enrolled high school students made a total of 8,216 visits during the 2002–2003 school year. High school A registrants were 48% male; however, females made 72% of all visits. The age distribution of SBHC users was 32% ages 14–15; 50% ages 16–17 and 18% ages 18–19. Additionally, 39% of the students made one visit, 31% made two visits and 21% made three visits. Fifty-six percent of the visits were made by students with no health insurance.

High school B registrants were 37% male, with 63% of all visits made by females. SBHC users were 43% ages 13–15; 43% ages 16–17 and 14% ages 18–19. Additionally, 53% of the students made one visit; 22% made two visits and 10% made three visits, while 13% made 4 or more visits. Forty-five percent of the visits were made by students with no health insurance.

Types of Visits

High school A had 1,222 enrolled students who made 4,374 visits in the 2002–2003 academic year. Of the 1,971 medical visits, 15% were for comprehensive health care, 21% acute/walk-in complaints, 26% reproductive health and 38% medical follow-up. Additionally, there were 757 health education, 798 mental health and 848 first aid visits. Referrals included 64 for medical specialty care, 19 for gynecologic specialty care and 5 for radiological studies.

High school B had 868 enrolled students who made 3,842 visits in the 2002–2003 academic year. The 1,880 medical visits were 20% comprehensive care, 20% medical follow-up, 20% acute/walk-in complaints and 40% reproductive health. Additionally, there were 734 mental health, 625 health education and 603 first aid visits. At this site, referrals included 80 for medical specialty care, 12 for gynecologic specialty care and 23 for radiological studies.

A review of 472 comprehensive health examinations as outlined in Table 1, revealed medical and psychosocial risk factors including asthma, a family member with HIV, nutrition issues, sexuality-related concerns, substance use and violence exposure. For purposes of comparison, Table 2 describes the psychosocial risk factors noted in archival information dated 1988.

SBHC Service Highlights

Medical

Because these SBHCs provide a full range of medical services, students are able to return to class immediately following treatment for an acute illness. For example, each academic year approximately 35 students are seen with symptoms of acute asthma; they are able to return to class following nebulizer treatment 85% of the time. Similarly, students who test positive for a sexually transmitted disease (STD) experience

TABLE 1
2003 Medical and Psychosocial Risk Factors

Factors	High School A (n=231)	High School B (n=241)
Asthma	17%	16%
Family member with HIV	11%	9%
Ever left back?	6%	17%
Think one is overweight	30%	32%
Vomit	2%	6%
Binge	7%	14%
Didn't eat all day	15%	25%
Sexually active	35%	43%
Attracted to same sex	3%	7%
Ever had STD?	7%	5%
Ever smoked cigarettes?	14%	38%
Ever smoked marijuana?	13%	24%
Ever drank alcohol?	38%	53%
Suicidal ideation	14%	23%
Touched/forced sex	7%	10%
Witnessed violence	37%	33%
Family history of diabetes	62%	43%
Overweight and obese	33%	31%

All students enrolled must have parental consent. STD = sexually transmitted disease

TABLE 2
1988 Psychosocial Risk Factors

Factors	School A	School B
Single parent home	55%	62%
Receive public assistance	30%	33%
Minimal access to health care	79%	65%
Current marijuana use	13%	13%
Current cocaine use	6%	17%
Current crack use	6%	4%
Recent drunkenness	23%	17%
Personal problems	41%	36%
Sadness/depression	44%	43%
Has had sex	43%	48%
No birth control last sex	58%	52%

All students enrolled must have parental consent.

little or no delay in treatment, as it is on-site and easily accessible. The rate of chlamydia was 4% in the 2002–2003 academic year. The 20% of students with abnormal pap smears were referred for colposcopy at our back-up facility, the Adolescent Health Center. A closer look at our students at risk for type 2 diabetes in High School A revealed that 62% had a family member with diabetes, 12% with acanthosis nigricans, and 18% with hypertension. In addition to medical assessment, students at risk for type 2 diabetes receive one-to-one nutrition assessments and referral to the "What's Really Good??!" fitness program.

Mental Health

On-site mental health services and their immediate availability for crisis intervention allow teenagers to engage in individual, family and group treatment before problems become so severe that they interfere with their education. Mental health referrals come from the medical service provider, school faculty and students themselves. Common diagnoses include post-traumatic stress disorder, anxiety disorder, and dysthymia, as well as adolescent adjustment disorder. Social workers lead groups dealing with the teenage issues of independence, peer pressure, decision making, and rights and responsibilities. The social workers also serve as a resource to school faculty; in addition to participating in guidance committees, they provide faculty in-service counseling on such issues as detecting depression, ensuring confidentiality and reporting abuse.

Health Education

Individualized and classroom health education services are an important addition to the primary and secondary prevention efforts of our SBHCs. An NYSDOH-funded Healthy Choices Initiative begun in 1998 was designed to reduce nutrition abnormalities, enhance fitness, and further violence prevention by implementing classroom workshops. Examples include healthy cooking classes provided by professional chefs from Metropolitan area restaurants, which were begun to teach students to prepare healthy, low-fat foods. A community garden program was initiated to have students grow and harvest fresh vegetables. A linkage formed with the Adolescent Health Center Violence Prevention Program provided sessions on teen relationship abuse, sexual assault, sexual abuse, and violence prevention strategies.

The "What's Really Good??!" program includes nutrition education and behavioral components integrated into physical education classes, in an effort to decrease type 2 diabetes risk factors. In addition to providing 45 minutes of active exercise, this program teaches strategies of self-monitoring, creating options, reframing negative thoughts, successful recovery from a relapse, and the benefits of accountability in achieving proper nutrition and regular physical activity. The tobacco prevention/cessation programs at the SBHCs use individualized "stages of change" counseling to assess and meet students' needs. Additionally, a parent-teen workshop focusing on tobacco and media literacy takes place annually. The SBHCs are well positioned to develop special initiatives to address the public health concerns of this age group.

Discussion

This 20th year of service highlights some unique features of the SBHC model of multidisciplinary health care delivery to teenagers. SBHCs provide care that is easily accessible, comprehensive in scope and supportive of educational goals. This model of health care delivery differs significantly from the traditional school nurse or physician's office model, in that it is comprehensive in nature, yet flexible enough to respond to specific population needs. Students who present to the SBHC are seen by the entire team, if appropriate, and are thus provided access to a broad safety net when facing difficult issues.

A review of the psychosocial issues acknowledged by teens and outlined in Tables 1 and 2 underscores the need for the type of care the comprehensive SBHC model can deliver.

While a snapshot of the risk factors in 2003 indicates that sexual activity has decreased somewhat, the issues of HIV, and eating and obesity have come to the forefront. SBHCs remain in a unique position to address these issues, because they can do so in a confidential manner and are integrated with students' daily educational environment. Most teens have difficulty assessing the long-term consequences of their action realistically and are therefore more likely to use services that are available on a spontaneous basis.

SBHCs improve access for confidential visits concerning issues less easily addressed at more conventional health care sites (7). Confidentiality is an essential component of access to some health services that teens need, for problems such as substance abuse, STDs or unintended pregnancy. Studies describing and comparing SBHC users to nonusers report that students at high risk for medical and psychosocial problems use the centers or are willing to use them for both routine and sensitive issues (1, 8–13). SBHC users are more likely than nonusers to be medically underserved and to receive SBHC services that are appropriate to address their problems (2, 9, 10, 14, 15). Reproductive health, the most controversial aspect of care, is offered by a number of sites in a variety of ways, e.g., 24% dispense contraception, 64% provide birth control counseling and 60% provide on-site treatment of STDs (1).

Although enrollment in a managed care organization (MCO) would seemingly eliminate the need for SBHC access, data indicates that this secondary access point reduces the use of after-hours care. A three-year Denver study comparing students who were MCO patients enrolled in an SBHC with students enrolled in the MCO alone indicated that the SBHC cohort had more health visits per year (5.33–5.00 vs. 3.4–3.9) but made 38–55% fewer after-hours care visits (16). Also, 96.5% of mental health visits and 100% of substance abuse treatment visits were made by adolescents with access to the SBHC (8). In contrast, only 3% of youths who attended schools with an SBHC utilized the MCO for behavioral health care (8). During this study, a greater proportion of students with access to both an SBHC and the MCO (80%) had one or more health supervision visits to the SBHC than did youth with access to the MCO alone (8). Our sites provide an important secondary access point for teenage-specific issues, for teens who have regular providers. Medically significant information is shared with these providers (with teen and parent consent) in order to prevent duplication of services, although the overwhelming majority of teens seen at our SBHC sites have no identified primary care provider. Studies also suggest that SBHCs significantly contribute to access to medical specialty services for those teens who need them (2). SBHC team members build upon their hospital and community networks to coordinate care and facilitate referrals, despite serving young people who may be uninsured or underinsured.

For many years SBHC staff have noted that their enrollees completed educational goals despite significant medical and mental health problems. However, there have been relatively few studies correlating school performance and SBHC use. One such study, of students attending an alternative high school in North Carolina, found that those who used the SBHC were significantly more likely to stay in school and graduate to the next grade; in fact, those who used the SBHC were nearly three times as likely to stay in school. This relationship was reportedly to be strongest for black males, but true for black females as well (17). SBHCs also decrease absenteeism on the day of illness by providing expeditious on-site treatment for a range of medical problems, from asthma exacerbation (18) to dysmenorrhea, and facilitating the student return to class.

The presence of an SBHC provides school faculty with a valuable opportunity to collaborate with a medical provider, mental health professional or health educator, by referring students who present concerns in the classroom setting, including acute asthma in the physical education class, suicidal ideation presenting in an essay for English class, and sexual abuse presenting to a guidance counselor. Faculty, students and parents participate in community advisory boards, which help ensure the relevance of the SBHC program to the health needs of the school population.

These SBHCs serve as training sites where adolescent medicine fellows, pediatric residents, medical students, social work interns, nurse practitioner students, and medical assistant students learn first hand about the important role schools play for the teenage patients they serve. Trainees are provided experiences that underscore health promotion, illness prevention, treatment and advocacy, while focusing on a patient's social, community and cultural context. Annually, the Adolescent SBHC program provides more than 1,000 hours of training. The multidisciplinary staff also demonstrates for teens the many professions and career paths that exist in health care.

At this time, more challenges remain for SBHCs, including further definition and evaluation of the SBHC's role in health promotion and disease prevention, continued integration into the nation's health care system, and securing long-term financial sustainability (1, 19). Studies have indicated that school-based health centers are effective in increasing young people's access to care, making it important to keep these programs viable and relevant to adolescent health care needs.

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Update in Atherothrombotic Disease

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Abstract

Crucial advances in our understanding of the pathogenesis of atherothrombosis, defined as atherosclerosis and its thrombotic complications, have been achieved during the past two decades. The historical hypothesis of pathogenesis ("lipid accumulation") has evolved to integrate several factors contributing to the initiation and evolution of this complex disease. Endothelial dysfunction is considered to be the earliest event in atherogenesis. Inflammation and apoptosis play critical roles in its progression and onset. Tissue factor is postulated to be a central actor in determining plaque thrombogenicity. A hyperreactive state of the blood ("vulnerable blood") may be responsible for one-third of all the acute coronary syndromes. This review will discuss emerging concepts in the pathogenesis of and therapeutic approaches to atherothrombotic disease.

Key Words: Atherothrombosis, atherosclerosis, antithrombotic therapy, coronary artery disease, acute coronary syndromes, tissue factor, inflammation, apoptosis, endothelial dysfunction.

Atherosclerosis and Atherothrombosis

ATHEROSCLEROSIS, the leading cause of mortality in the Western world, is a diffuse process that starts in early childhood and progresses asymptomatically through adult life. Later in life, it is clinically expressed as ischemic coronary syndromes (or coronary artery disease, CAD), stroke, transient ischemic attack (TIA) and peripheral artery disease (PAD). From the clinical point of view, we should envision this disease as the same pathologic entity that affects different vascular beds. From a pathologic point of view, it is characterized by intimal thickening owing to cellular and lipid accumulation that is due to an imbalance in lipid influx and lipid efflux. It affects the intima of large and medium arteries, including the aorta, as well as the carotid, coronary, and peripheral arteries (1, 2). Secondary changes may occur in the underlying media and adventitia, particularly in advanced disease stages. Fatty streaks have been found in the intima of infants (3). They progress to fibroatheroma by developing a cap of smooth muscle cells and collagen. Atherosclerotic lesions can progress without compromising the lumen because of compensatory vascular enlargement (positive remodeling) (4). Importantly, lipid-rich lesions (culprit lesions) leading to acute coronary syndromes are often mildly stenotic due to the significant positive remodeling, and are therefore not detectable by angiography (5, 6). Plaque disruption and subsequent thrombus formation is responsible for the onset of most acute coronary syndromes and strokes. The magnitude of the thrombotic process triggered upon plaque disruption is modulated by different elements that determine plaque and blood thrombogenicity: local shear rate, tissue factor, apoptotic microparticles, circulating monocytes, etc. The atherosclerotic and thrombotic processes appear to be interdependent and could therefore be integrated under the term "atherothrombosis," a broader term that includes both atherosclerosis and its thrombotic complications.

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Socioeconomic Impact

Coronary artery disease and its thrombotic complications, stroke, transient ischemic attack and peripheral artery disease (PAD) are the leading cause of morbidity and mortality in developed countries. The annual incidence of stroke, TIA and CAD together in the United States is approximately 3.03 million. The annual incidence of emergency department (ED) visits for the evaluation of chest pain is estimated to be approximately 8 million (7). The total cost of CAD in the U.S. for 2002 was $111.8 billion: direct costs $58.2 billion, and indirect costs $53.6 billion (Fig. 1) (8). It can be predicted that the socioeconomic burden of atherothrombosis will continue to increase as the result of several factors: (a) increased survival during acute phases of ischemic disease, transforming acute patients into chronic patients (e.g., ischemic cardiomyopathy, heart failure, post-stroke disability, chronic intermittent claudication); (b) aging of the population; (c) increase in health-related costs; and (d) "Westernization" of the lifestyle in developing countries (e.g., smoking, diabetes, diet, stress, etc.).

"Vulnerable" or "High-Risk" Plaque

Despite a common physiopathologic pathway, atherosclerotic lesions are very heterogeneous, and the "high-risk plaque" of each vascular bed has unique characteristics. Insights into the disease have advanced beyond the notion of progressive occlusion of the coronary artery, to the recognition that plaque disruption and superimposed thrombus formation are the leading causes of acute coronary syndromes and cardiovascular deaths. Therefore, plaque composition (as a determinant of risk of disruption), rather than luminal stenosis, has become the major determinant of this disease (9, 10).

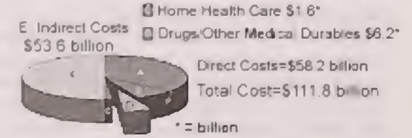

Fig. 1. Cost of coronary heart disease in the United States: year 2002 (8).

Histologically, these rupture-prone (also called vulnerable or high-risk) lesions consist of a large core of extracellular lipid, a high density of macrophages containing lipids, reduced numbers of vascular smooth muscle cells (SMCs), and a thin fibrous cap. Thus, it is not surprising that these plaques are less stable and have a higher propensity to rupture than the fibrous, collagen-rich plaques. Plaque disruption usually occurs at the weakest point ("shoulder"), frequently where the cap is thinnest and most heavily infiltrated with inflammatory cells (11). Once the plaque is disrupted, the highly thrombogenic lipid-rich core, abundant in tissue factor (TF), is exposed to the bloodstream, triggering the formation of a superimposed thrombus that leads to vessel occlusion and subsequent ischemic symptoms distal to the occlusion (12, 13).

In contrast to most of the high-risk coronary plaques, the high-risk carotid plaques are significantly stenotic, heterogeneous, and very fibrous. The disruption is often caused by an intramural hematoma or dissection that probably relates to the systolic stroke of blood against the resistance they offer because of their stenotic condition (14). Although the lipid accumulation in the carotid arteries is quite diffuse, a recent study reported the presence of ruptured lipid-rich plaques in patients with TIA and stroke (15).

Thoracic aorta high-risk plaques frequently contain a high proportion of extracellular lipids and are characterized by a shift toward greater macrophage content relative to SMCs in the cap. At autopsy, aortic plaques from persons who died of ischemic heart disease often have ulceration and mural thrombosis (16). Recent aortic plaque characterization by magnetic resonance imaging confirmed their lipid-rich composition (17).

The plaques at high risk for acute ischemic syndromes of the lower extremities appear to be very stenotic and fibrotic (18). Nonetheless, as distinguished from carotid artery disease, available evidence suggests that in PAD, plaque stenosis associated with hyperthrombogenicity of the systemic blood seems to be a more important contributor to acute ischemic syndromes (sudden ischemic pain, gangrene). This is suggested by the high prevalence of diabetes, cigarette smoking and dyslipidemia (19), which are known to cause a hyperthrombogenic state of the blood (20, 21).

Emerging Concepts in Pathogenesis

Views of the pathophysiology of atherothrombosis have evolved substantially over the past 2 decades. The etiological theory of atherothrombosis has now been widened to include complex biologic processes—such as inflammation, apoptosis, tissue factor (TF) physiology, and the behavioral sciences—in determining the onset of acute ischemic events (Fig. 2).

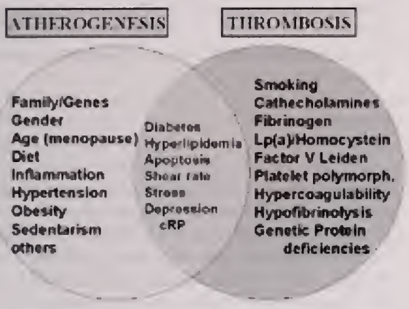
ATHEROGENESIS
THROMBOSIS
Family/Genes
Gender
Age (menopause)
Diet
Inflammation
Hypertension
Obesity
Sedentarism
others
Diabetes
Hyperlipidemia
Apoptosis
Shear rate
Stress
Depression
cRP
Smoking
Cathecholamines
Fibrinogen
Lp(a)/Homocystein
Factor V Leiden
Platelet polymorph.
Hypercoagulability
Hypofibrinolysis
Genetic Protein deficiencies

Fig. 2. The circle called atherogenesis includes the most accepted risk factors involved in the development of atherosclerosis. The circle called "Thrombosis" contains a list of prothrombotic factors. In the overlap area are shown the elements involved in both atherosclerosis and thrombosis (i.e., atherothrombosis).
cRP = C-reactive protein

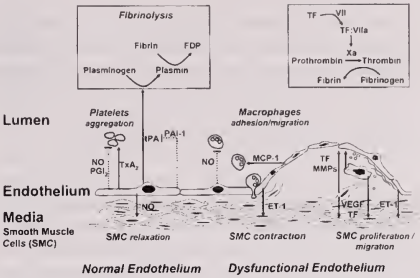
Fibrinolysis
Fibrin
FDP
Plasminogen
Plasmin
TF
VII
TF:VIIa
Xa
Prothrombin
Thrombin
Fibrin
Fibrinogen
Lumen
Platelets aggregation
tPA
PAI-1
NO
PGI2
TxA2
Macrophages adhesion/migration
NO
MCP-1
TF
MMPs
Endothelium
NO
ET-1
VEGF
TF
ET-1
Media
Smooth Muscle Cells (SMC)
SMC relaxation
SMC contraction
SMC proliferation / migration
Normal Endothelium
Dysfunctional Endothelium

Fig. 3. Impact of endothelial dysfunction on atherogenesis. ET-1 = endothelin-1; FDP = fibrin-degradation products; MCP-1 = monocyte chemoattractant protein-1; MMPs = matrix metalloproteinases; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor; PGI_2 = epoprostenol; SMC = smooth muscle cell; TF = tissue factor; T_XA_2 = thromboxane A_2; VEGF = vascular endothelial growth factor

Endothelial Dysfunction

Endothelial dysfunction is a systemic, reversible disorder considered to be the precursor that initiates the atherosclerotic process (22, 23). It is characterized by a reduction of the bioavailability of vasodilators, in particular nitric oxide (NO), and an increase in endothelium-derived contracting factors (Fig. 3). This imbalance leads to an impairment of endothelium-dependent vasodilation, the hallmark of endothelial dysfunction. A dysfunctional endothelium promotes lipid and cell permeability, lipoprotein oxidation, inflammation, SMC proliferation, extracellular matrix deposition or lysis, platelet activation, and thrombus formation (24). The endothelium regulates the production of prothrombotic and antithrombotic factors, growth factors and vasoactive substances. The clear predilection for lesion formation at arterial branching points indicates the importance of local rheologic conditions in atherosclerosis. Furthermore, endothelial cell gene expression is modulated by acute changes in flow profiles (25). A dysfunctional endothelium generates a proatherogenic environment by creating a proinflammatory, proliferative and prothrombotic milieu that favors atherogenesis (25). In addition, platelet-derived mediators such as serotonin induce vasoconstriction in the presence of a dysfunctional endothelium (26). Moreover, vasoconstrictor response to these stimuli is increased by endothelin-1 (27), concentrations of which are elevated in the plasma of patients with early and advanced atherosclerosis (28) as well as in culprit lesions (29). Endothelial dysfunction is involved in the recruitment of inflammatory cells into the vessel wall and in the initiation of atherosclerosis. Endothelial cells produce cytokines and express adhesion molecules (e.g., selectins, and vascular and intercellular cell adhesion molecules) and assist leukocytes and other blood-derived cells in "homing" and infiltration. Monocytes migrate into the subendothelium, where they transform into macrophages and modulate inflammatory reactions and the secretion of chemoattractants.

Many of the cardiovascular risk factors, including hyperlipidemia, hypertension, diabetes, and smoking are associated with overproduction of reactive oxygen species or increased oxidative stress, both of which reduce vascular NO bioavailability and promote cellular damage (30). Hence, increased oxidative stress is considered to be a major mechanism involved in the pathogenesis of endothelial dysfunction and may serve as a common pathogenic mechanism of the effect of risk factors on the endothelium (30, 31). In summary, endothelial dysfunction contributes to enhanced plaque vulnerability, may trigger plaque rupture, and favors thrombus formation: it thus may be viewed as an important causal factor for several aspects of atherothrombotic disease.

Inflammation and Atherothrombosis

There is a growing body of evidence supporting the link between inflammation and atherothrombosis (32). Early in atherogenesis, patches of arterial endothelial cells begin to express on their surface selective adhesion molecules that bind to various classes of leukocytes (Fig. 3). In particular, vascular cell adhesion molecule-1 (VCAM-1) binds precisely to the types of leukocytes found in early human and experimental atheroma, the monocyte and T lymphocyte. Not only does VCAM-1 expression increase on endothelial cells overlying nascent atheroma, but mice genetically engineered to express defective VCAM-1 show interrupted lesion development (33). Once attached to the endothelium, the leukocytes penetrate into the intima. In addition to oxidized low-density lipoprotein, monocyte chemoattractant protein-1 (MCP-1) appears to be responsible for the direct migration of monocytes into the intima at sites of lesion formation (34). Once they are in the arterial wall, the blood-derived inflammatory cells participate in and perpetuate a local inflammatory response. The macrophages express scavenger receptors for modified lipoproteins, permitting them to ingest lipids and become foam cells.

Inflammatory processes not only promote initiation and evolution of atherosclerosis, but also contribute decisively to acute thrombotic complications of atheroma. The activated macrophages abundant in atheroma can produce proteolytic enzymes (e.g., matrix metalloproteinases, MMP) capable of degrading the collagen that lends strength to the plaque's protective fibrous cap, rendering that cap thin, weak, and susceptible to rupture. An overexpression of all three human interstitial collagenases (MMP-1, 8, and 13) has been demonstrated in atheroma (35). In addition, γ-Interferon arising from the activated T lymphocytes in the plaque can halt collagen synthesis by SMCs, limiting its capacity to renew the collagen that reinforces the plaque (36). Macrophages also produce tissue factor, the major procoagulant and trigger to thrombosis found in plaques. Inflammatory mediators regulate tissue factor expression by plaque macrophages, demonstrating an essential link between arterial inflammation and thrombosis (37).

Elevated values of inflammatory biomarkers, such as C-reactive protein (CRP) (38), interleukin-6 (IL-6) (39), serum amyloid A (40), soluble ICAM-1 (41), and CD40L (42) commonly accompany CAD. Their elevation correlates in some series (43) with adverse prognosis and may reflect the contribution of inflammation as an instigator of atherosclerotic plaque instability.

Tissue Factor

Tissue factor (TF) is known to be a potent initiator of coagulation cascade, and its presence in atherosclerotic plaque suggests its potential role as a key determinant of plaque thrombogenicity (44–46) (Fig. 4). Tissue factor antigen, TF activity, as well as TF mRNA have been identified in different cell types within the atheroma, including endothelial cells (EC), vascular SMCs, and especially cholesterol-enriched macrophages (foam cells) (47). TF antigen is also detected in the extracellular matrix of atherosclerotic plaque and is thought to be derived largely from macrophages present in plaque, with a minor contribution of vascular SMC and EC. Several studies have demonstrated that TF is most abundant in the shoulder region and acellular, lipid-rich core of the plaque (48). Recently, the majority of TF expression within human plaques was found to be in areas of high density of apoptotic cells and microparticles (49). Furthermore, TF activity in the acellular lipid core was found mainly on apoptotic microparticles of monocytic and lym-

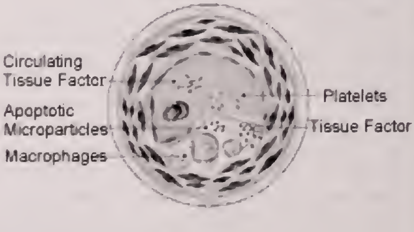

Fig. 4. Disrupted atherosclerotic plaque. The presence of tissue factor and apoptotic microparticles may be responsible for the thrombogenic potential of the disrupted atherosclerotic plaque. Circulating tissue factor is strikingly increased in patients with cardiovascular risk factors; hence it may also play a role in the formation of the thrombus upon atherosclerotic plaque disruption.

phocytic origin (49). These microparticles with procoagulant potential are rich in phosphatidylserine, providing in this way the appropriate phospholipid environment required for TF activity (50). All this evidence highlights the importance of TF in thrombus formation upon plaque disruption; hence, it is attractive to consider TF as a new pharmacologic target.

Apoptosis and Atherothrombosis

The role of apoptosis in atherothrombosis can be described at two separate levels, at the site of the plaque and in the circulation. Apoptosis in atherothrombotic disease involves all cell types (51). Within and around the necrotic core, as well as in the fibrous cap, there is an accumulation of foam cells and nuclear fragments staining positive for terminal deoxynucleotidyl transferase neck end labeling (TUNEL) (52, 53).

Despite the initiation of the cell death process, apoptotic cells are involved in the inflammatory process through further recruitment of other inflammatory cells. For example, the externalization of phosphatidylserine by apoptotic cells, which can be detected with Annexin V (54), has the immunogenic potential to activate neighboring cells for phagocytosis (55).

Mallat and Tedgui (50) reported a clear association between apoptosis and inflammation. They demonstrated coexistence of inflammation and apoptotic cells in areas of plaque rupture that resulted in exposure of a high fraction of apoptotic cells and debris to the circulation (56). It is believed that, besides having immunogenic and inflammatory characteristics, apoptotic cells possess a highly thrombogenic potential (57, 58). Thus, they are postulated as one of the determinants of plaque thrombogenicity.

It has been demonstrated that apoptosis coexists with high levels of TF expression within the atherosclerotic plaque (48). TF is functional on the cell surface and its activity is highly dependent on the presence of phosphatidylserine (PS) (59). Since PS exposure is associated with apoptosis, it has been suggested that apoptosis may be partly responsible for TF activation within plaque. Recently, Hutter et al. (60) demonstrated the co-localization of TF and apoptosis in macrophages within lipid-rich human atherosclerotic plaques and, in addition, showed *in vitro* that a significant percentage of macrophages exposed to oxidized low-density lipoprotein (Ox-LDL) undergoing apoptosis expressed TF. There is further evidence that apoptosis in different cell types promotes procoagulant activity.

Interestingly, the prothrombotic potential of different apoptotic cells is not only confined locally to atherosclerotic plaque, but is also present in circulation. Mallat et al. (61) initially demonstrated the presence of high levels of shed membrane apoptotic particles in extracts from atherosclerotic plaques, but not from the underlying arterial wall. Later, the same group showed the presence of high levels of endothelial membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes, implying that they might participate in the generation and perpetuation of intracoronary thrombi (56). This indicates a major role of apoptosis in atherothrombosis following plaque rupture.

Peroxisomal Proliferator-Activated Receptors

Peroxisomal proliferator-activated receptors (PPARs) are steroid hormone nuclear receptors that act as ligand-activated transcription factors controlling the expression of specific target genes, which in turn regulate a variety of cellular functions (Fig. 5). The subfamily member PPAR-γ plays a central role in adipogenesis and lipid metabolism and is highly expressed in endothelial cells, SMCs, lymphocytes, and

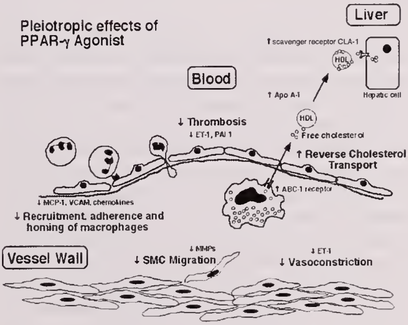

Fig. 5. Pleiotropic effects of peroxisomal proliferator-activated receptors (PPARs). PPARs are steroid hormone nuclear receptors that control a variety of cellular functions that may have the potential for inducing plaque regression and stabilization.
ABC-1 = adenosine triphosphate-binding cassette transporter-1; A_{PO} -A1 = apolipoprotein A1; CLA-1 = class B type 1 human homolog; ET-1 = endothelin-1; HDL = high-density lipoprotein; MCP-1 = monocyte chemoattractant protein-1; MMPs = matrix metalloproteinases; PAI-1 = plasminogen activator inhibitor-1; SMC = smooth muscle cell; VCAM = vascular cell adhesion molecule

macrophages (62). In early atheromas, PPAR-γ was found in foam cells and SMCs (63, 64). Several studies reported that PPAR-γ activators might reduce plaque inflammation (65, 66) by inhibiting activation of many proinflammatory genes responsible for plaque development and growth. PPAR-γ agonists also inhibit expression of adhesion molecules (67) and cytokines (66), and reduce production of matrix metalloproteinases (MMPs) (64). Evidence indicates that PPAR-γ activators can decrease thrombogenicity by reducing plasminogen activator inhibitor-1 (PAI-1) and fibrinogen concentrations, thus improving fibrinolysis (68). In addition, PPAR-γ agonists may reduce production of endothelin-1, a potent vasoconstrictor and an important atherogenic stimulus. Crucially, PPAR-γ agonists enhance reverse cholesterol transport by upregulating the genes responsible for scavenger receptor class B type I human homolog (CLA-1) (69), adenosine triphosphate-binding cassette transporter-1 (ABC-1) and apolipoprotein A1 (Apo A1), therefore facilitating efflux of free cholesterol from the plaque and its transport to the liver. These *in vitro* data suggest that PPAR-γ agonists have the potential pleiotropic effects required to induce plaque regression and stabilization.

Microembolization and Microvascular Obstruction

Plaque rupture, occurring either spontaneously or during percutaneous coronary interventions, results in the release of prothrombotic material into the coronary circulation, which may embolize the microvascular bed. This phenomenon leads to a markedly reduced myocardial function, whereas coronary blood flow remains unchanged or is even increased. The increase in coronary blood flow is attributed to vasodilation of adjacent nonembolized vessels in response to adenosine release from the microembolized myocardium. The loss of contractile function in microembolized myocardium is attributed to inflammatory processes, in particular tumor necrosis factor-α (70).

Evidence for the occurrence of distal embolization in the pathogenesis of acute coronary syndrome (ACS) is found in autopsy studies demonstrating the presence of platelet and platelet/fibrin microemboli in the cardiac tissue of patients who died suddenly or of acute myocardial infarction (MI). Prevalence in these studies was 50–80% (71). These platelet aggregates are likely to represent emboli rather than merely platelet hyperactivity, because they are located distal to epicardial coronary arteries containing thrombus overlying a ruptured atheromatous plaque instead of being distributed more evenly in the myocardium. In addition, embolization of cholesterol and atheromatous material has been demonstrated (71). In the setting of acute MI, the presence of distal embolization is assessed clinically by looking for the presence of microvascular obstruction after reperfusion. This is known as the "no-reflow" phenomenon. Because it is demonstrated very early in the course of MI, microvascular obstruction is most likely caused by embolization rather than by edema or reperfusion injury (72).

Depression

Since established cardiovascular risk factors do not account for all patients who develop ACS events, the search for "nontraditional" risk factors has emerged (Fig. 2). Many of the immune-inflammatory factors playing a role in plaque instability have been associated with psychological factors. Depression is associated with enhanced activation of platelets and with enhanced release of β-thromboglobulin (73). Depression is also associated with elevated interleukin-6 (IL-6), which can activate platelets as well. In a recent study (74), it was demonstrated that 5-hydroxytryptamine (5-HT)-mediated platelet reactivity is significantly increased in depressed patients relative to nondepressed matched controls. However, it should be noted that adenosine diphosphate (ADP; a non 5-HT agonist) did not differentiate depressed patients from their controls, as had been previously reported by other investigators (75).

"Vulnerable Blood" and "Vulnerable Patient"

In one-third of the cases of ACS, particularly in sudden coronary death, there is no disruption of lipid-rich plaque but only superficial erosion of markedly stenotic and fibrotic plaque (76). Thrombus formation in such cases may depend on a hyperthrombogenic state triggered by systemic factors. Indeed, systemic factors, including elevated low-density lipoprotein (LDL) cholesterol, cigarette smoking, hyperglycemia, hemostasis and others, are associated with increased blood thrombogenicity (44).

Elevated LDL cholesterol levels have been found to increase blood thrombogenicity and growth of thrombi under defined rheology conditions (77, 78). Reducing LDL cholesterol levels with statins was shown to decrease thrombus growth by approximately 20% (78). The question is, to what extent does such an antithrombotic effect, for example with statins (documented in large prospective clinical trials), contribute to the reduction of total vascular events, including death, coronary events, and stroke (79, 80)?

Smoking increases sympathetic nerve activity (81) and, therefore, catecholamine release, which may potentiate platelet activation and increase fibrinogen levels. Catecholamine-dependent effects in the circulating blood could explain not only the increase in the incidence of sudden death and acute cardiovascular events after emotional and physical stress, but also the circadian distribution of these events (82).

Diabetic patients, especially those with poorly controlled diabetes, have increased blood thrombogenicity (21). Platelets from patients with diabetes have been shown to have increased reactivity and hyperaggregability due to increases in a variety of activation-dependent adhesion proteins on their surfaces (83). Abnormal platelet function is reflected by increased platelet consumption and increased accumulation of platelets on the altered vessel wall.

Recent observations indicate that the hyperthrombogenic states associated with high LDL cholesterol, cigarette smoking, and diabetes may share a common biological pathway: activation of leukocyte-platelet interactions associated with the release of TF and thrombin activation. Specifically, more leukocyte-platelet aggregates circulate in the blood of patients with diabetes mellitus than in that of nondiabetic patients. The prothrombotic state in diabetes is also associated with an increased expression of monocyte procoagulant activity in the presence of diabetic microalbuminuria. The increased procoagulant activity in diabetes is attributed to leukocytes, which may in part activate the TF pathway (84, 85) and contribute to high blood thrombogenicity in diabetic patients (83).

Recent studies have found increased levels of circulating TF antigen in patients with cardiovascular disease (86). Circulating TF has been associated with increased blood thrombogenicity in patients with unstable angina (87) and chronic coronary artery disease. Blood levels of TF have also been shown to predict outcome in patients with unstable angina (88).

As previously described, lipid-rich atherosclerotic plaques contain TF associated with macrophages within the lesion (47) which may account, in large part, for the high thrombogenicity of these lesions. Tissue factor has also been identified within thrombi formed in the coronary arteries. In addition, specific inhibition of the TF pathway by TF pathway inhibitor (TFPI) significantly reduces plaque thrombogenicity (45). The TFPI is usually expressed in the adventitial layer of large arteries, and in atherosclerotic vessels TFPI is expressed by macrophages in focal areas in the plaque. Local production of TFPI may regulate procoagulant activity and thrombotic events within atherosclerotic plaques (89).

In addition to apoptotic macrophages and microparticles from atherosclerotic plaques, activated monocytes in the circulating blood seem to be a source of TF microparticles and may represent the result of activation by the previously mentioned risk factors and others, thus contributing to thrombotic events. Within the context of the possibly proinflammatory or prothrombotic effects on the circulating blood exerted by high LDL cholesterol, cigarette smoking and diabetes, there is increasing evidence that circulating monocytes and white blood cells may be involved in TF expression and thrombogenicity (86). Indeed, the predictive value for coronary events of high levels of C-reactive protein (CRP) may be a manifestation of such systemic phenomena (39).

C-reactive protein (CRP), similar to fibrinogen, is a protein of the acute-phase response and a sensitive marker of low-grade inflammation. Increased levels of CRP have been reported to predict acute coronary events (38), and CRP seems to be a useful marker in the prediction of thrombotic events. Whether CRP reflects the inflammatory component of atherosclerotic plaques or of the circulating blood, and whether it is a surrogate marker or a biologically active element in plaque development of thrombus formation at the site of the atherosclerotic vessel, are not known (90). Nevertheless, recent studies support the hypothesis that CRP is an activator of blood monocyte and vessel-wall endothelial cells (91).

New Antithrombotic Therapies

Understanding the molecular mechanisms that underlie atherothrombotic disease has been critical in developing optimal pharmacologic therapies. Given the key role of thrombosis, pharmacologic therapy has sought to provide potent inhibition of both platelet aggregation and coagulation cascade. Traditionally, antiplatelet therapy with aspirin (92) and clopidogrel, and anticoagulation therapy with unfractionated heparin (UFH) (93), low molecular weight heparin (LMWH) and warfarin, have been the cornerstone of management of patients with atherothrombosis. Despite the beneficial effects of these agents, they have limitations, and novel antithrombotic agents have been developed to address these limitations. Given the critical role of TF in atherothrombosis, different therapeutic approaches directed toward inhibiting the TF pathway have been investigated (Fig. 6).

Three groups of agents inhibiting TF pathway are being developed. The first group consists of specific TF inhibitors, the second contains factor Xa inhibitors, and the third includes direct thrombin inhibitors (DTI). Within the first group, recombinant TFPI is available as a recombinant drug. In order to avoid some bleeding complications associated with systemic administration of recombinant TFPI, transfer of human tissue factor pathway inhibitor gene has recently been accomplished by using an adenovirus as a vector (94). Another novel therapeutic approach is the inhibition of TF gene transcription. The nuclear factor NF-kB pathway is a key transcriptional mechanism in induction of the TF gene. Dithiocarbamates, specific inhibitors of this pathway, reduced TF expression in preclinical studies (95). The blockade of TF-induced thrombin generation was studied by using inactivated factor VIIa, a competitive inhibitor of TF-dependent factor X activation. In both animal models and studies in humans, thrombus formation was prevented by infusing inactivated factor VIIa (96). Studies in animals and more recently in humans have demonstrated the efficacy of TF monoclonal antibodies in reducing thrombosis (97). A peptide with a mode of action comparable to TFPI is a nematode anticoagulant protein c2 (NAPc2). A recombinant form of NAPc2 was tested in an animal model and showed promising results (98).

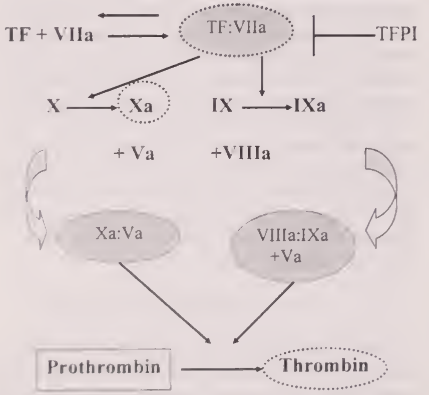

Fig. 6. Tissue factor pathway and potential therapeutic targets. As described in the picture, the binary complex TF:VIIa is of critical importance in initiating the coagulation cascade, and therefore it represents a very attractive pharmacologic target (within dashed circle).
TF = tissue factor; TFPI = tissue factor pathway inhibitor

Selective inhibitors of factor Xa can be classified as direct, those which bind directly to factor Xa, or indirect, such as fondaparinux, which require antithrombin III for their action.

The DTIs include hirudin, bivalirudin, and a second generation of agents, called active site inhibitors. Melagatran, together with its oral prodrug (ximelagatran) is the most extensively investigated of this last group of drugs. Recent studies on TF pathway inhibitors are summarized in the Table (45, 78, 94 – 120).

Conclusion

In this review we wanted to emphasize the following concepts:

1. Atherothrombosis should be used to define atherosclerosis and its thrombotic complications. This term refers not only to the classical coronary syndromes, but also to cerebrovascular and peripheral artery diseases.

2. The concept of "vulnerable blood" explains those clinical situations characterized by thrombus formation in the presence or absence of plaque disruption.

3. Inflammation and endothelial dysfunction are of paramount importance as determinants of "vulnerability" of flowing blood.

4. High levels of circulating tissue factor activity have been associated with those subpopulations of CAD patients particularly prone to thrombotic complications (diabetics, smokers, dyslipidemic).

5. Vascular cells undergoing apoptosis seem to be a source for observed increase of circulating TF activity in these subpopulations.

6. Inhibition of tissue factor metabolic pathway is being introduced as a novel and effective antithrombotic target.

TABLE

Summary of Recent Studies on Tissue Factor Pathway Inhibitors

Therapy	Mechanism of Action	Model	References
Tissue Factor Inhibitors			
Tissue factor pathway inhibitor (TFPI)	Direct binding to factor Xa	Animal	Oltrona L et al. (99)
	Inhibition of TF:VIIa complex	Animal	Han X et al. (100) Bajaj MS and Bajaj SP (101)
		In vitro	Badimon JJ et al. (45)
Gene transfer of TFPI	Local expression of TFPI	Animal	Atsuchi N et al. (102) Golino P et al. (94)
Monoclonal antibodies	Inhibition of TF activity	Animal	Ragni M et al. (103) Annex BH et al. (97)
		In vitro	Rauch U et al. (78)
Dithiocarbamates	Inhibition of TF gene transcription	Animal	Drollinger AG et al. (104) Bohrer H et al. (95)
Active site-inactivated factor VIIa (Approved for clinical use)	Competitive inhibition of TF-dependent activation of factor Xa	Animal *In vitro*	Banner DW et al. (96) Jang Y et al. (105)
Nematode anticoagulant protein c2 (In clinical development)	Inhibition of TF:VIIa complex	Animal Human	Rote WE et al. (98) Lee A et al. (106)
Factor Xa Inhibitors			
Tick anticoagulant peptide	Direct inhibition of factor Xa	Animal *In vitro*	Beimond BJ et al. (107) Orvim U et al. (108)
Antistatin	Direct inhibition of factor Xa	Animal	Ragosta M et al. (109)
DX9065 (In clinical development)	Direct inhibition of factor Xa	Human	Shimbo D et al. (110)
Fondaparinux (Approved for clinical use)	Indirect inhibition of factor Xa	Human	Turpie AG et al. (111)
Thrombin Inhibitors			
Hirudin (Approved for clinical use)	Direct thrombin inhibitor	Human	OASIS-1 & 2 (112)
Bivalvidurin (Approved for clinical use)	Direct thrombin inhibitor	Human	CACHET (113)
Argatroban (Approved for clinical use)	Active site thrombin inhibitor	Human	ARGAMI (114)
Melagatran (In clinical development)	Active site thrombin inhibitor	Human	METHRO I, II, III (115–117)
Ximelagatran (In clinical development)	Active site thrombin inhibitor	Human	METHRO I, II, III (115–117)
		Human	SPORTIF I, II, III (118, 119)
		Animal	Carlsson S et al. (120)

Despite the advances in our understanding of the pathophysiology of this disease and the improvement of the therapeutic armamentarium, atherothrombosis continues to be the leading cause of mortality in most of the Western world.

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Abstracts

The following abstracts were presented at the Annual Resident Research Day on May 28, 2003 at the Jersey City Medical Center, Jersey City, NJ and at the Annual Resident Research Day on May 28, 2003 at the Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Jersey City Medical Center

Prospective Evaluation of the Efficacy of Blood Culture (BC) in the Evaluation of Fever in the Gynecologic Population. C. Liburd and C. Gagliardi. Department of Ob/Gyn, Jersey City Medical Center, Jersey City, NJ.

At Jersey City Medical Center blood cultures (BC), CBC, urine cultures and chest x-ray are routinely performed as part of the assessment of gynecology patients with primary temperature elevation of >101°F on admission or in the perioperative period. To evaluate the efficacy and cost effectiveness of BCs in this population, all patients during a 7-month period from July 2002 to January 2003 were prospectively evaluated. The degree of temperature elevation, HIV status, leukocyte count, culture results and final diagnosis were noted. Additionally, the surgical site (if any), IV site, chest x-ray results and final diagnosis were recorded.

Results: Fifty-four samples were collected from 27 patients. Twenty patients were perioperative and seven were hospitalized for fever. Of the 27 patients, 24 were HIV negative and 3 were of unknown status. Fever renged from 101°F to 103°F. One urine culture was positive for group B Strep. No positive chest x-rays were noted. None of the BCs were positive for either contaminants or pathogens.

Conclusion: The routine use of BCs for fever greater than 101%F in the gynecologic population is an effective component of the fever evaluation. The cost of processing one BC vial is $63.00, or $252 per patient. The use of BC should be more selective in this patient population.

Discharge Planning and Length of Survival among Hospice Patients. A. Reddy[1], H. Ison[2], S. Titapiwatanakun[1], and M. Reisner[1]. [1]Department of Medicine, Jersey City Medical Center; Jersey City, NJ; and [2]Quality Management and Performance Improvement Coordinator, Comfort Care Hospice, Pompton Plains, NJ.

Objective: To compare the length of survival among terminally ill patient receiving hospice care at home and in health care facilities.

A group of 206 patients referred for hospice care between February 2002 and January 2003 were studied. Fifty-six patients were from home and 150 patients were from health care facilities. The medical diagnosis of these patients included cancer, dementia, HIV, CVA, chronic obstructive pulmonary disease, generalized, cardiac and renal diseases. A t-test indicated a significant difference in the mean length of survival between home and health care facility hospice patients, $p<0.0005$. The length of survival of patients receiving hospice in home, a mean of 91.07 days, was shown to be significantly longer than hospice patients in health care facilities, a mean of 41.36.

Discussion: Increased length of survival of terminally ill patients receiving home hospice care highlights the need for interventions that reduce physical and psychological distress. Studies that provide insight into potential factors that influence survival are few. In three randomized, controlled studies, psychosocial interventions resulted in longer survival times for patients with breast cancer, lymphoma and malignant melanoma. Other research findings on increased social support and sense of control have shown decreasing health risks and lower mortality rates in the elderly. Underlying mechanisms for these outcomes are unknown although possible explanations could include health maintenance behaviors and effects on immune function. Applied to discharge planning process, these findings promote the use of home hospice care for the optimal quality and duration of life for the terminally ill patient.

Bacterial and Fungal Bloodstream Infections in Neonates at Jersey City Medical Center—2002. S. Uko[1], C. Doria[1], S. Alsheikh[1], and C. Strand[2]. Departments of [1]Pediatrics and [2]Pathology, Jersey City Medical Center, NJ.

The 2002 microbiology records for positive blood cultures in neonates (ICN, ITN and NN) showed 47 neonates with blood stream infections including 43 (91.5%) unimicrobial cases, 3 (6.5%) poly and unimicrobial and 1 (2%) polymicrobial cases. The most common organisms (or organism groups) were coagulase-negative staphylococci (CNS), yeasts and gram-negative enteric (GNE) bacteria. Recurrent infections were seen in 19 patients, 13 with two separate episodes, one with 3 episodes, 2 with 4 episodes and 3 with ≥5 episodes.

This data show that the most common microbial agents causing neonatal blood stream infection are CNS, yeasts, and GNE and that 19 (40.2%) had recurrent episodes of blood stream infection.

Safety of Video Fiberoptic Bronchoscopy Guided Percutaneous Dilatational Tracheostomy. A. Devarajan[1], C. Vasquez[1], P. Ledereich[2], and D. Flores[1]. Departments of [1]Medicine and [2]Surgery, Jersey City Medical Center, Jersey City, NJ.

Objective: To study the safety, complications and future direction for the minimally invasive procedure, “video fiberoptic bronchoscopy guided percutaneous dilatational tracheostomy.”

Over a period of one year, 12 patients with respiratory failure requiring tracheostomy underwent the above procedure in the operating room using video-assisted bronchoscopy for the initial identification and maximal visibility of the proper site of tracheal puncture and insertion of the guide wire. Appropriately sized straight Portex set was used for the procedure. Complications such as intra- and peri-operative bleeding, dislodgement, air leaks, pneumothorax, infection, subcutaneous emphysema, and edema surrounding the site were studied. Only one patient developed an air leak due to smaller size of tracheostomy tube. No other complications were noted in any of our patients. No death directly related to the procedure has occurred and the morbidity due to the procedure was minimal.

Conclusion: This is a safe minimally invasive procedure with low complication rate. The same procedure can also be accomplished at bedside in an ICU setting with low complication rate.

The Clinical Conundrum of Monoamniotic Monochorionic Gestation. C. Carter[1] M. Esedebe[1], and C. Strand[2]. Departments of [1]Ob/Gyn and [2]Pathology, Jersey City Medical Center, Jersey City, NJ.

Introduction: Naturally occurring twin pregnancies occur in approximately 1/100 pregnancies. Eighty percent of twin gestations are dizygotic and 20% are monozygotic. Monoamniotic, monochorionic (MM) twin gestations are extremely rare occurring in <1% of monozygotic twins. The fetal mortality rate is 40–60%, due primarily to cord entanglement.

Case: Within the last 4 years, 3 cases of MM twins were seen at Jersey City Medical Center. A 19-year-old G1P1001 presented to the emergency department at 12 weeks gestation with vaginal bleeding. She spontaneously passed stillborn MM twins with entangled umbilical cords. A 19-year-old G1P0 at 15 weeks gestation presented with an inevitable abortion. She delivered MM twins with entangled umbilical cords. A 30-year-old G1P0 was diagnosed with MM twins in the second trimester. Serial ultrasounds and Doppler flow studies demonstrated cord entanglement and decreased umbilical blood flow. She was admitted to labor and delivery at 28 weeks for continuous fetal monitoring and delivered viable male infants by cesarean section at 32 weeks.

Discussion: MM twins is a rare form of twin gestation with a high mortality rate. Early recognition of MM twins can be difficult, but is imperative to management. Once gestation approaches viability, antenatal management varies and is controversial. Despite intensive antenatal monitoring, there is no assurance of a good outcome. Timing of delivery must balance the risk of sudden fetal death vs. fetal maturity.

Ovarian Ectopic Gestation—A Rare Ectopic Gestation. S. Yousry, D. Campbell, and P. Brug. Department of Ob/Gyn, Jersey City Medical Center, Jersey City, NJ.

The incidence of ectopic pregnancy (EP) has recently increased to 19.7/1,000 pregnancies. The majority of ectopic pregnancies (98%) are tubal gestations, but ectopic gestations do occur at other sites.

Case: A 32-year-old G4P3 with 7 weeks of amenorrhea presented to the emergency department complaining of lower abdominal and shoulder pain. Physical examination disclosed a pale, diaphoretic, woman with tachycardia, orthostatic changes, and an acute abdomen. Serum __hCG was 3824 mIU. Findings at exploratory laparotomy included: 1,000 cc hemoperitoneum, normal fallopian tubes bilaterally, normal uterus and a normal right ovary. On the left ovary, a hemorrhagic cyst was bleeding freely. The ovary was partially resected to remove tissue and secure hemostasis. Patient received 2 units packed red blood cells and rapid decline in serum__-hCG was noted.

Discussion: Ovarian ectopic pregnancies (OEP) are exceedingly rare (0.2% of ectopic gestations), and are seldom diagnosed preoperatively. Intraoperatively, OEPs may easily be confused with a ruptured corpus luteum cyst. OEPs are associated with greater hemoperitoneum and more frequently require blood transfusion. Although final diagnosis requires examination of the pathology specimen, the surgeon must be vigilant. Normal fallopian tubes at the time of surgery for hemoperitoneum do not exclude the diagnosis of ectopic pregnancy. Correct diagnosis is important for patient counseling and future reproduction.

Atrial Flutter in the Perinatal Age. I. Bass[1], S. Uko[1], S. Puvabanditsin[1], E. Garrow[2], and M.J. Torres[1]. Department of [1]Pediatrics and [2]Surgery, Jersey City Medical Center, Jersey City, NJ.

Atrial flutter (AF) is an uncommon form of tachycardia in infancy. It is a potentially lethal arrhythmia. The management of this order is difficult and controversial. The pharmacologic treatment poses a challenge to clinicians and electrophysiologists. We present a neonate with atrial flutter The tachyarrhythmia was successfully terminated with digoxin administration. The infant survived with no long-term cardiac sequelae.

Rare Case of Idiopathic Distal Renal Tubular Acidosis. A. Reddy, S. Titapiwatanakun, and M. Reisner. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: Distal renal tubular acidosis (RTA) in the elderly is usually associated with other autoimmune disorders or laxative abuse. Idiopathic distal RTA in the geriatric population has been rarely documented. A 75-year-old female presented with progressive generalized weakness of one-day duration without any associated symptoms of vomiting, diarrhea, fever, respiratory distress, dysphagia or palpitations. Patient denied laxative or NSAID abuse. Pertinent findings on physical examination included proximal muscle weakness and decreased deep tendon reflexes. Laboratory evaluation revealed hypokalemia (2.0 meq/L) and a normal serum anion gap. Urinalysis was remarkable for a pH of 7.0 and a positive urinary anion gap. PH was 7.30 on arterial blood gas. All the work-up into other causes of normal anion gap hyperchloremic metabolic acidosis with hypokalemia was negative and the patient was considered to have idiopathic distal RTA. Patient responded well to potassium supplements and was discharged on oral bicarbonate supplements.

Conclusion: A literature search revealed only one other case report of Idiopathic Distal RTA in the geriatric population. We report the second case.

Esophageal Perforation Subsequent to Anterior Cervical Spine Fixation. S. Titapiwatanakun and P. Weissman. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

A 67-year-old white male, with laryngeal carcinoma S/P total laryngectomy, radiation therapy, and permanent tracheostomy about 15 years ago, presented with dysphagia, mainly to solid food, for 2 days, without odynophagia, choking, chest pain or heartburn. History included a fracture of C5–C7 spines S/P anterior cervical spine plating 2 years ago. Physical examination revealed a pale looking male, no lymphadenopathy, tracheostomy tube in place, otherwise unremarkable.

He also had an esophago-gastro-duodenoscopy (EGD) that demonstrated an old food bolus with necrotic tissue at the proximal esophagus, a metallic structure at the posterior esophagus below the food particle, and a large hiatal hernia. Chest and neck CT revealed a metallic structure in the cervical esophagus with a mass effect at the base of tongue. Cytology study from brushings was negative for malignant cells. Because of his chronically ill status, the patient received conservative treatment with an open gastrostomy tube placement, nothing by mouth, and a course of parenteral antibiotics.

Esophageal perforation is usually due to medical procedure (pneumatic esophageal dilatation and EGD), paraesophageal surgery, spinal trauma or foreign body ingestion. This patient had an esophageal perforation resulting from transmural erosion of cervical spine plate fixation into the esophagus. This is a rare complication of anterior cervical surgery and may be caused by either pressure sores or plate migration.

Hypogammaglobulinenemia with Normal or Increased IgM (Hyper-IgM Syndrome). M. Farkhondeh, S. Sodhi, and I. Belem. Department of Pediatrics, Jersey City Medical Center, Jersey City, NJ.

X-linked hyper-IgM syndrome (a clinical variant of hypogammaglobulinemia) is a severe immunodeficiency disorder with significant cellular involvement and high mortality rate. Opportunistic infections with low virulence organisms such as *Pseudomonas* species are associated with high mortality. Patients may have clinical neutropenia and develop oral and rectal ulcers. Responses to childhood immunization are also poor. These patients frequently respond well to infusion of immunoglobulins.

Case: A 21-month-old black male presented with fever, diarrhea of 7 day duration associated with a skin rash of the trunk, extremities and peri-anal ulcerated lesions (0.5×0.5 cm). Significant medical history included pneumonia, otitis media and pre-orbital cellulites. Patient's condition worsened and developed clinical signs of septic shock requiring intensive care. Blood and wound cultures grew *Pseudomonas aeroginosa*. Laboratory work-up revealed neutropenia (absolute neutrophyl count [ANC] 156), microcytic anemia, decreased level of (immunoglobulin) IgG, IgA and IgE, normal IgM level and normal T-cell count. Tests for HIV, syphilis, and stool culture were negative. Patient was treated with appropriate antibiotics along with infusion of immunoglobulins and was discharged home.

Discussion: The hyper-IgM syndrome is a rare, immune deficiency disorder resulting from defects in the CD40 ligand gene that prevents it from delivering an activation signal to antigen-presenting cells. Defects in molecules involved in CD40 signaling has been shown to cause other forms of hyper-IgM. These newly identified defects emphasize the importance of interaction between CD40 and its ligand in immunity and the role of these molecules in the pathogenesis of immune deficiency. With genetic defects in the hyper-IgM syndrome identified, it is possible to diagnose patients definitively, perform genetic screening, and delineate the clinical manifestation for this syndrome. Further research may lead to novel therapeutic options for these patients with this condition.

Queens Hospital Center

Advanced Liver Cancer in a Patient with a High Alpha Fetoprotein: Case Report.

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Case Presentation: A 53-year-old man with a history of diabetes mellitus, depression, and a positive hepatitis surface antigen initially presented with nausea/vomiting and diarrhea for three months. He had developed jaundice, ascites, and weight loss of 20 pounds over a period of six months. His liver was slightly tender and enlarged, 1.5 inches below the right costal margin, and the spleen was just palpable. He was found to have increased serum liver enzymes: alanine aminotransferase (ALT), 151 U/L; aspartate aminotransferase (AST), 310 U/L; alkaline phosphatase (AP), 280 U/L; and gamma-glutamyl transpeptidase (GGT), 394 U/L. He had high bilirubin levels (total bilirubin 7.8 g/dL and direct bilirubin 5.1 g/dL). Prothrombin time/activated partial thromboplastin time (PT/aPTT) and INR were within normal limits. Repeated hepatitis profile showed positive HbeAb and HbcAb. The patient had multiple therapeutic paracenteses. The ascitic fluid was bloody, but was negative for malignant cells, culture was negative, total protein was 1.1 g/dL, albumin < 1.0 g/dL, glucose 259 mg/dL, lactic dehydrogenase (LDH) 60 U/L and alpha-fetoprotein 4650.4 ng/mL (normal, 0–8.5). Abdominal ultrasound was positive for ascites, bilateral pleural effusion and hepatosplenomegaly. The liver was heterogeneous and the presence of a mass could not be excluded. Abdominal/pelvic CT scan with IV contrast confirmed the liver mass, measuring approximately 17.5 cm in the widest diameter and contained multiple small hypodense areas, suggestive of possible necrosis. Following an informed discussion with the patient a consensus was reached that palliative care would be the desired method of management. The patient declined a liver biopsy.

Discussion: Our patient was found to have positive HbsAg, HbeAb and HbcAb, ascites fluid, a very high alpha-fetoprotein, and a huge hepatic mass on CT scan. Oncology consult was requested for this patient with presumed advanced hepatocellular carcinoma (HCC) because of the clinical scenario, positive HbsAg, very high alpha-fetoprotein and a large liver mass on CT scan. However, no pathological diagnosis was made. Although the mainstay of therapy is surgical resection, several other treatment modalities may also have a role. The patient's hepatic reserve often dictates therapeutic options. Treatment options for HCC are divided into surgical therapies (i.e., resection, cryoablation, and orthotopic liver transplantation), and nonsurgical therapies (i.e., percutaneous ethanol injection, radiofrequency ablation, transarterial chemoembolization, chemotherapy and radiation). Considering the very advanced stage of the disease (the large size and abnormal liver function tests, surgery was precluded), a grim prognosis, and low-to-uncertain effectiveness of nonsurgical therapies, the patient chose to have only supportive/palliative treatment.

Antiphospholipid Antibody Syndrome Presenting as Deep Venous Thrombosis and Pulmonary Embolism in a Patient with Human Immunodeficiency Virus—A Case Report and Review of Literature.

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Introduction: Although antiphospholipid antibodies (aPL) are detected in patients with HIV disease, the clinical manifestations of antiphospholipid syndrome (APS) are extremely rare. We describe a woman with HIV and elevated aPL who presented with deep venous thrombosis (DVT) of the leg and pulmonary embolism (PE). This finding contradicts the general belief that these antibodies are not clinically significant in patients with HIV.

Case Report: A 46-year-old female diagnosed with HIV disease six months ago, on antiretroviral medications presented with complaints of pain and swelling of the right calf of 3 weeks duration.

Right leg pain and swelling started about 3 weeks ago, pain worsening with ambulation and movement. Patient denied trauma, recent travel or fever. On the second day of hospitalization, she complained of shortness of breath without cough or chest pain. She had two uncomplicated pregnancies and no history of miscarriages. She never took oral contraceptives. There was no family history of rheumatic disease, vascular disease or clotting disorders.

Her right leg was swollen from knee to ankle. The maximum circumference of right calf was 41.5 cm and of left calf was 39.3 cm. The calf was mildly tender without erythema or warmth, no cord was palpable and Homans' sign was negative.

She had normal prothrombin time, a high normal partial thromboplastin time of 35.2 (24.6–35.4) seconds. Anticardiolipin antibody IgG was high at 46.08 (<22), IgM was high at 19.41(<10) and lupus anticoagulant (LA) with simplified dilute Russell viper venom test (RVVT) was positive. Factor V Leiden mutation analysis was negative. Rheumatology investigation was negative.

Duplex imaging of the right lower extremity showed minimal flow in the popliteal artery, consistent with DVT. Ventilation perfusion scan done the day after admission showed ventilation-perfusion mismatch with a segmental perfusion defect in the left lung, suggestive of intermediate probability for pulmonary thromboembolism. Arterial blood gases done at the same time showed P_{O2} of 72, PCO_2 of 38 with a high A-a gradient of 30, confirming the diagnoses of PE given the clinical presentation.

Clinical presentation and laboratory findings were consistent with antiphospholipid syndrome presenting as DVT and PE. The patient was started on anticoagulation and has remained free of any further complications of APS.

Discussion: Antiphospholipid antibodies, namely the LA and the anticardiolipin antibody (aCL), are a family of autoantibodies directed predominantly against negatively charged phospholipids. They were first identified in patients with syphilis and are often found in patients with systemic lupus erythematoses. The principal manifestations of APS include venous and arterial thrombosis, thrombocytopenia and recurrent abortions. The laboratory diagnosis of APS is based on elevated IgG and IgM aCL levels and a positive LA test, which is a functional test of the aPL antibodies as in our patient.

There are case reports of DVT and PE in HIV/AIDS patients with normal aCL and LA levels. The higher risk for DVT in these patients is attributed to a wide range of comorbidity associated with HIV disease. Hypercoagulability, opportunistic infections, malignancies and malnutrition make these patients more prone to develop DVT. By contrast, although a significant percentage of patients with HIV disease have aPL antibodies, the clinical expression of APS in these patients is extremely rare. To the best of our knowledge only three such cases have been previously reported in the English literature.

Conclusion: We recommend that clinicians maintain a heightened awareness of suspicion of APS in HIV patients. HIV patients who have thrombotic events should be investigated for aPL. If these antibodies are present, anticoagulation therapy must be maintained lifelong in order to prevent the recurrence of a life-threatening thrombotic event.

Four-Year Retrospective Analysis Examining Adherence to Five of The American Diabetes Association (ADA) Guidelines for Diabetic Care. D. Noel, S. Yennurajalingam, D. Reich, and I. Sachmechi. Department of Medicine, Mount Sinai Services, Queens Hospital Center, Jamaica, NY.

Objective: To examine adherence to the American Diabetes Association guidelines for the five main parameters in diabetic care in Queens Hospital Center and to determine if there was an improvement in the four years of follow-up.

Methods: We performed a retrospective chart review of 250 patients with type 1 and type 2 diabetes who were followed in the Diabetes Clinic at Queens Hospital Center from 1998–2001. Data was collected on five parameters: lipid profile, HBA1c, ophthalmology examination, nephropathy assessment and whether the patient was receiving aspirin. Data was analyzed for each year to examine adherence to the ADA guidelines and the comparison was made for the 4-year period to determine improvement in adherence.

Results: Clinical data from the 250 patients for the first year (1998) showed that 67% had HBA1c, 65% had lipid profile, 31% were receiving aspirin, 28% had urine protein assessment and 47% had ophthalmology examination. In the second year (1999), 81% had HBA1c, 80% had lipid profile, 50% were receiving aspirin, 49% had urine protein assessment and 58% had ophthalmology examination. In the third year (2000), 91% had HBA1c, 89% had lipid profile, 58% were receiving aspirin, 55% had urine protein assessment and 70% had ophthalmology examination. In the last year (2001), 92% had HBA1c, 91% had lipid profile, 70% were receiving aspirin, 70% had urine protein assessment and 73% had ophthalmology examination (see Table below).

Conclusion: Diabetes mellitus affects over16 million Americans and the ADA guidelines provide a standard for diabetic care. Recommendations include HBA1c twice yearly for controlled diabetes and quarterly for uncontrolled diabetes, lipid profile annually, dilated eye examination by eye care specialist annually, test for microalbuminuria annually and aspirin therapy in patients over 30 years of age. Analysis of the data collected showed that there was an improvement in adherence to the ADA guidelines over the four-year study period, in Queens Hospital Center, with over 70% of patients having all five parameters in the last year of study.

Hemorrhagic Complications of Outpatient Anticoagulation Therapy: One Hospital's Experience. T. Wren[1], B.H. Mobo, Jr.[2], and I.J. Tan[3]. [1]Medical student, Ross University, Domenica; [2]Yale University, New Haven, CT; and [3]Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Objective: To compare the admission rates and bleeding complications of warfarin therapy before and after the introduction of an anticoagulation clinic.

Design and Setting: Retrospective cohort study at a municipal teaching hospital in New York City.

Methods: Chart review was conducted on 91 consecutive admissions over a 24-month period with a diagnosis of adverse effects of anticoagulants. Main outcomes include demographic characteristics, admission rates, severity of bleeding, intensity of treatment, and length of hospital stay. Outcome measures were compared 12 months before and after the introduction of anticoagulation clinic.

Results: Of the 91 admissions, 0.57% (39/6861) occurred before and 0.76% (52/6825) after the introduction of an anticoagulation clinic (p=0.175). These account for 19.7% (39/198) vs. 22.8% (52/228) of patients on warfarin therapy (p=0.435), respectively. Most were African-American and Guyanese of Indian extraction. Mean admission INR levels were 6.08 (3.15–11.6) vs. 8.6 (3.9–16.5) (p=0.445). While results were not statistically significant, more patients were admitted with bleeding complications (46.2% vs. 38.5%, p=0.462) that required more intense treatment (46.2% vs. 42.3%, p=0.715) before the anticoagulation clinic. However, mean hospital stay was longer after the introduction of the anticoagulation clinic (4 vs. 5 days, p=0.588). No admission due to thrombotic events or fatality due to supratherapeutic anticoagulation was noted during the study period (see Table, p. 213).

Conclusion: Introduction of an anticoagulation clinic in our hospital center was associated with less severe bleeding complications but more hospital admissions and longer hospital stays. These observations were not statistically significant and reflect the lack of power or small number of cases. Thus a longer study observation period may be useful to confirm these.

TABLE

Results (in percents)

	HBA 1c	Lipid Profile	Aspirin Therapy	Nephropathy Assessment	Ophthalmology Examination
1998	67	65	31	28	47
1999	81	80	50	49	58
2000	91	89	58	55	70
2001	92	91	66	70	73

TABLE

Results for 91 Admissions

Outcome Measures	Before warfarin Clinic	After warfarin Clinic	P value
Age, Mean (Range)	62 (33–88)	65 (27–96)	0.407
Sex (Female/Total)	19/39 (49%)	30/52 (40%)	0.395
Race	10/39 (26%)	21/52 (40%)	0.142
African-American Guyanese	9/39 (23%)	10/52 (19%)	
# Events/Total Admissions	39/6861 (0.567%)	52/6825 (0.7619%)	0.175
Proportion of Moderate + Severe + Potentially Fatal Intensity of Treatment	18/39 (46.2%)	22/52 (42.3%)	0.715
INR, Mean (Range)	6.08 (3.15–11.6)	8.6 (3.9–16.5)	0.445
Mean Hospital Stay in days (Range)	4 (2–28)	5 (1–33)	0.588

Hypocalcemia-Induced Myocardial Ischemia and Reversible Cardiac Dysfunction. H. Manne, A. Premasiri, G. Peress, A. Nosrati, I. Sachmechi, and D. Reich. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: The central role of calcium in the contraction of the myocardial cell is well known from animal and human studies. Case reports describe hypocalcemic cardiac failure in conditions like uremia, dialysis, and primary hypoparathyroidism. We report the case of a patient with severe hypocalcemia presenting with myocardial injury and reversible cardiac dysfunction.

Case Report: A 54-year-old African-American woman with a medical history of alcohol abuse, with no other significant cardiac or other medical problems and not taking any medications, was hospitalized for shortness of breath, profuse sweating and muscle cramps. Physical examination showed no signs of cardiac or pulmonary disease. A positive Trousseau's sign was elicited along with coarse tremors of the hands. The chest x-ray showed a normal cardiac silhouette and the EKG showed sinus tachycardia, T wave inversions in lead II, III, AVF and v2–v6, and ST segment elevations in v3–v6. The corrected QT interval measured between 450–470 ms. Significant initial laboratory values included serum calcium 4.8 mg/dL (8.5–10.5), magnesium 0.5 mg/dL (1.7–2.7), potassium 3.2 mg/dL (3.5–5.3), ionized calcium 2.7 mg/dL (4.5–5.3), serial troponin I values of 1.49 ng/mL (<1.5), 2.46, and 3.97; creatine kinase (CK) 491 units/L (26–155), creatine kinase MB isoenzyme 3.41 ng/mL (<6 ng/mL), creatine kinase MB isoenzyme fraction of 0.7% (<6%), aspartate aminotransferase (AST) 207 units/L (2–40), lactate dehydrogenase (LDH) 512 units/L (90–224), serum albumin 2.8 g/dL (3.3–5.3) with normal serum creatinine, thyroid function tests, serum pH and phosphorus level. Further testing revealed an intact parathyroid hormone of 501 pg/mL (12–72) and a 25 hydroxy vitamin D level of 8 ng/mL (10–68). Initial echocardiogram revealed mild left ventricular hypertrophy with hypokinesis of the apex, left middle ventricle, and right ventricle apex and an ejection fraction of 25%. Cardiac catheterization revealed normal coronary arteries. After replacing calcium and magnesium for 10 days the serum values were normalized. A follow-up echocardiogram was performed which showed improved left ventricular and right ventricular function with a normal ejection fraction. The follow-up EKG showed reversal of ST segment elevations to normal.

Discussion: Unlike skeletal muscle, cardiac muscle contraction is heavily dependent on calcium coming from the T tubules, which have a much greater diameter and volume than the T tubules of skeletal muscle. The sarcoplasmic reticulum of cardiac muscle is less developed than that of skeletal muscle and does not have enough calcium by itself to provide full contraction. The calcium of the T tubule in turn depends on the extracellular calcium concentration, as the T tubule opens into the interstitium. The extracellular calcium plays an important role in the strength of contraction in cardiac muscle fibers. Studies have shown improvement of cardiac parameters after acute and chronic treatment of hypocalcemia.

Summary: This patient presented with acute shortness of breath, profuse diaphoresis and signs of increased neuromuscular excitability on physical examination. She was found to have profound hypocalcemia as well as hypomagnesemia and mild hypokalemia. The EKG and troponin I values suggested myocardial injury and the initial echocardiogram suggested significant ventricular dysfunction. In accordance with the role extracellular calcium plays in myocardial contractility, it seems very plausible that reversible myocardial dysfunction could be caused by hypocalcemia as occurred in our patient. Hypomagnesemia is also a recognized cause of myocardial dysfunction and could also have contributed to this patient's congestive heart failure on presentation. Hypokalemia, on the other hand, is not a well-established cause of myocardial dysfunction.

In this case alcoholic cardiomyopathy was not the cause of the initial left ventricular dysfunction, since the follow-up echocardiogram revealed normal LV function. The link between hypocalcemia and myocardial injury is less clear, though coronary vasospasm has been offered as an explanation.

Conclusion: Hypocalcemia can cause myocardial injury and reversible cardiac dysfunction.

Kawasaki Disease in an Adult. R. Khodzinskiy, M. Gill, A. Rehman, and E. Restrepo. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Kawasaki disease (KD) is an idiopathic, infantile, acute febrile systemic disease, also known as mucocutaneous lymph node syndrome. It is the most common cause of acquired heart disease in children in the Western countries. We report the case of a young adult who experienced signs and symptoms of KD.

Case Report: A 19-year-old Hispanic man presented with complaints of fever, chills and skin rash for one week and hematuria for one day. One week prior to admission he developed a painful swelling on the right side of the neck, followed a day later, by fever, chills and a diffuse, non-pruritic skin rash involving face, trunk, and extremities, including palms and soles. By day five, right neck swelling disappeared. On day six, he noticed blood-tinged urine, prompting him to come to the hospital.

On physical examination, blood pressure was 103/55 (non-orthostatic), temperature was 103.8°F, heart rate was 108 and respiratory rate was 18 with a diffuse erythematous, nonpalpable rash, more pronounced on the extremities, palms and soles without nail changes. There was bilateral conjunctivitis but without purulent discharge, a "strawberry" appearing tongue, and erythematous, mildly enlarged tonsils.

White blood cell count was 21 on admission, falling to 9.5 after 15 days; hemoglobin was 13.6 on admission, subsequently 9.8; and platelets were 242,000, subsequently 775,000.

The initial blood urea nitrogen/creatinine was 50/3.6, then 7/0.9. There was proteinuria. By day 4 proteinuria disappeared. Erythrocyte sedimentation rate was 45 on day 3 and 145 on day 9. Alkaline phosphatase was 135 U/L, aspartate aminotransferase 53 U/L, alanine aminotransferase 73 U/L, T bilirubin 4.9 mg/dL and direct bilirubin 3.2 mg/dL. Patient had high C-reactive peptide and 1-aminotrypsin levels. Hepatitis panel, Lyme Disease titer, Epstein-Barr virus antibody, leptospira antibody, serum protein electrophoresis, central spinal fluid, coagulations, reticulocyte count, and chest x-ray were normal. ECG on admission showed sinus tachycardia of 105, right bundle branch block.

The patient remained persistently febrile. By day four, the patient was noted to have nonpurulent, bilateral conjunctivitis with concomitant marked icteric sclerae and jaundice. Subsequently, he was noted to have firm, non-tender swelling on the dorsum of his hands, tender bilateral ankle swelling, a new onset of desquamation of the skin around his fingernails and toenails with proximal progression. Multiple blood cultures, urine culture and throat culture remained negative. Human immunodeficiency virus ribonucleic acid PCR second generation viral load was less than 50 copies/mL. By the 9th hospital day, the patient was still febrile, with persistent leukocytosis, increasing platelet count, progressive anemia, high erythrocyte sedimentation rate, C-reactive protein, alpha 1 antitrypsin, and sterile pyuria. At this point KD was considered, and treatment with high-dose aspirin (80 mg/kg/day) and IV immunoglobulin in a single dose of 2 g/Kg were started on day 10. After initiation of treatment, the patient became afebrile with gradually disappearing signs of inflammation.

Transesophageal echocardiogram on day 6 revealed borderline dilatation of the left ventricle with ejection fraction 55–60%, dilated right atrium and trace pericardial effusion. Serial, daily ECGs became normal. The patient was discharged on day 16 in stable condition.

The presentation of KD is polymorphous. The early manifestations of the disease share vast symptoms with many other similar conditions. With the progress of this disorder, the diagnosis of KD becomes more and more evident. Although the vast majority of described cases are in children, isolated case reports of KD in adults have been published.

Adults are less likely to suffer from the detrimental effects of the disease on the coronary arteries. Nevertheless, echocardiographic follow-up is advisable for adult patients with the disease.

Large Artery Disease Involvement in Systemic Sclerosis. C. Onwe and A. Opran. Department of Medicine, Queens Hospital Center and Mount Sinai School of Medicine, Jamaica, NY.

Vascular involvement in systemic sclerosis (SSc) has been well established. Distortion and obliteration of capillary loops and concentric intimal proliferation in arterioles and small arteries are associated with clinical findings such as Raynaud's phenomenom, pulmonary hypertension and renal ischemia. Large vessel involvement is less common in SSc and there are only few case reports regarding large arterial thrombosis in SSc; most cases are associated with the antiphospholipid syndrome (APS).

We report a patient with systemic sclerosis and small vessel disease involvement with Raynaud's phenomenom of the upper and lower distal extremities. Worsening of ischemic changes in the lower legs prompted angiographic evaluation of the large vessels which showed significant thrombosis of the superficial femoral arteries bilaterally. The patient underwent revascularization surgeries—left superficial femoral artery endarterectomy, thrombectomy and angioplasty, and right popliteal artery endarterectomy and angioplasty. Six years later she maintains a good functional status with preservation of the affected limbs. Our patient had evidence of new thrombosis in the absence of risk factors for coagulopathy such as the antiphospholipid syndrome. She also had no risk factors for peripheral vascular disease or accelerated atherosclerotic disease. After femoral popliteal bypass surgery and the use of warfarin she remained free of ischemic symptoms. Noninvasive vascular laboratory studies (ankle brachial index and Doppler) still show obstruction in the left dorsalis pedis and posterior tibialis and the popliteal arteries bilaterally but the grafts are patent. Thrombosis of a major artery can be a catastrophic complication in systemic sclerosis.

Large vessel involvement in systemic sclerosis should be promptly investigated in patients with worsening ischemia.

Metastatic Prostate Adenocarcinoma Presenting with Oligoarticular Septic Arthritis. S.A.S. Banigo, R. Paguia, and I.J. Tan. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Mount Sinai School of Medicine, Jamaica, NY.

Introduction: Polyarthritis may be a form of paraneoplastic syndrome while septic oligoarthritis has rarely been reported as an initial presentation of solid tumors. We report the case of a patient presenting with septic oligoarthritis due to *Staphylococcus aureus*, who also had polyarthralgias and who was later found to have metastatic carcinoma of the prostate gland.

Case Report: A 64-year-old African-American man with a history of treated pulmonary tuberculosis, a 50-pack-year smoking history, and 6 years of polyarthralgias involving the shoulders, elbows, wrist, hand, knees and ankles (relieved by acetaminophen and low-dose ibuprofen for 2 years, and recently treated with acetaminophen with codeine) was admitted with 10 days of pain and swelling of the right elbow and both knees, fever of 102%F and difficulty in walking.

Physical examination was remarkable for (a) mild swelling with diffuse tenderness over the right wrist, (b) right elbow pain on pronation associated with soft tissue swelling laterally, (c) mild pain in the left elbow and (d) warm knees with large effusions, pain, and decreased range-of-motion, but no erythema. Digital rectal examination revealed a hard prostate and the stool was positive for occult blood.

Serum prostate specific antigen was 14,000 ng/mL (0–4), serum alkaline phoshatase 152 mg/dL (30–115), total serum protein 7.4 g/dL (6.5–8.5), with albumin of 3.1 g/dL (3.3–5.3), erythrocyte sedimentation rate was 134 mm/hr (0–10), serum C-reactive protein was 26.2 mg/dL (0–0.8), rheumatoid factor was 578 IU/mL (0–20), and antinuclear antibody negative. X-ray of the hands showed minimal periarticular osteopenia, and a solitary subchondral cyst in the right carpal bone, but no joint space narrowing or erosions. X-ray of the knees revealed suprapatellar effusion of the left knee without evidence of fracture or osseous abnormalities. Synovial fluid from both knees yielded up to 150,000 leukocytes/high power field, low glucose level, and absence of crystals. Blood cultures and synovial fluid cultures were positive for *S. aureus*. Transesophageal echocardiogram was negative for vegetations. Abdominal sonogram showed an enlarged heterogeneous prostate gland and hepatosplenomegaly.

All signs of active synovitis resolved after a 6-week course of intravenous antibiotic (nafcillin) and repeated joint aspirations. Additional investigation revealed adenocarcinoma of the prostate on biopsy and widespread skeletal metastatic disease on bone scan. The patient was subsequently started on monthly leuprolide injection with resolution of the baseline symmetric polyarthralgias of 6 years.

Discussion: More than 80% of patients with rheumatoid arthritis (RA) would be expected to have x-ray signs of bony erosions within 2 years of symptoms. Our patient had 6 years of polyarthralgias without signs of erosions or joint space narrowing which makes RA highly unlikely. Rheumatoid factor (RF) positivity is a nonspecific test, and RF may be present in RA, or malignancy, among other clinical entities. We believe that our patient had symmetric polyarthritis as a form of paraneoplastic syndrome for 6 years, presented to medical attention when the joints were secondarily infected by *S. aureus*; later resolved with the treatment of prostate carcinoma.

Septic arthritis is usually acquired via hematogenous spread in the background of one or more risk factors such as malignancy, liver cirrhosis, bacteremia, RA, joint prosthesis, or intravenous drug abuse. Monoarticular in 90% of patients, the susceptible joints are often involved in decreasing order of frequency: knee, hip, elbow, shoulder and finger. Our case is unique since oligo- and polyarticular forms of arthritis are rare in patients with cancer.

Summary and Conclusion: We suggest that patients with metastatic adenocarcinoma of the prostate may be predisposed to septic arthritis by *S. aureus* at multiple sites. Symmetric polyarthralgias thought to be paraneoplastic syndrome responded to treatment for cancer, while the response of septic arthritis to antibiotics and repeat joint aspiration was excellent in our case. Clinicians should maintain a high index of suspicion for underlying metastatic malignancy when a patient presents with septic oligoarthritis, especially in the absence of RA.

Thyrotoxic Periodic Paralysis: Case Report. C. Onwe, I. Sachmechi, and D. Reich. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Thyrotoxic periodic paralysis (TPP) is an uncommon disorder characterized by simultaneous thyrotoxicosis, hypokalemia and paralysis occurring mainly in young men. It is more commonly associated with Graves disease but can also occur with toxic nodular goiter, thyroiditis, TSH-producing tumors and abuse of thyroid hormone. It occurs predominantly in young Asian men but has also been reported in other ethnic groups. We present a case of TPP in a 39-year-old Filipino man with Graves disease.

Case Presentation: A 39-year-old man from the Philippines with a history of hyperthyroidism receiving methimazole 5 mg daily presented with complaints of inability to walk. The patient reported that he woke up with cramps and pain in the thigh muscles and weakness of the lower extremities. He fell while attempting to get out of bed and was carried to the car by family members to be brought to the emergency room. The patient denied dizziness, chest pain, palpitations, shortness of breath, loss of consciousness, seizure or loss of sphincteric function. The patient had a similar episode of weakness and fall 2 months prior to this presentation, which resolved spontaneously. He denied a family history of similar illness or seizures. There was no history of trauma. The patient has been smoking half a pack of cigarettes per day for 20 years, drinks alcohol occasionally and denies drug use. He has no known drug allergies.

On examination, his blood pressure was 140/80 Mm Hg, pulse rate 80 beats per minute, respiratory rate 20, and temperature 98°F. He was alert and oriented; the thyroid gland was diffusely enlarged, non-tender, about 50 gm with a positive bruit. His muscle power was 3/5 bilaterally in all extremities and deep tendon reflexes were diminished. His speech was normal. Laboratory tests revealed the following abnormalities: serum potassium 2.3 meq/dL (3.5 – 5.0), magnesium 1.4 mg/dL (1.8 – 3.0), TSH <0.004 mu/L (0.4 – 6.0), triiodothyronine 453.87 ng/dL (61 – 181), thyroxine 14.6 ug/dL (4.5 – 12), free thyroxine 5.71 ug/dL (0.71 – 1.85). The electrocardiogram showed sinus rhythm at 92/min with u waves. The patient's symptoms resolved after potassium and magnesium replacement. The repeat potassium was 3.6 mmol/L and the repeat magnesium was 1.8 mg/dL. The patient was started on propranolol 20 mg p.o. tid and methimazole 30 mg p.o. daily.

Conclusion: Thyrotoxic periodic paralysis should be considered when young males present with sudden onset of severe lower extremity weakness. TPP can be prevented with maintenance of a euthyroid state. However, during the acute period of paralysis, treatment includes the use of propranolol, on the basis that it blocks the adrenergic effect of thyroid hormone, thus blocking the intracellular shift of potassium. Cautious administration of potassium to prevent arrhythmias may be employed.

An Unusual Case of Late Life Sarcoidosis. S. Muralidharan and C. Feiner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

We describe the case of an elderly woman who was diagnosed with sarcoidosis at the age of 79 and subsequently developed metastatic cancer that presented as ascites two years later. Review of the literature showed that sarcoidosis is rarely seen in patients over the age of 60 and could represent a systemic response to tumor antigens. We conclude that primary care physicians need to be cognizant of the association between sarcoidosis and carcinomas such as lymphoma, lung, prostate and ovary.

A 79-year-old African-American woman with a medical history of hypertension and osteoarthritis followed in our geriatric clinic since 1985 developed blurring of vision in the left eye in April of 1999. Ophthalmological evaluation revealed active uveitis, which was treated with topical steroids.

At the recommendation of the ophthalmologist, an investigation was performed to rule out systemic causes. Chest x-ray showed fibrotic and atelectatic changes in both lung fields suggestive of stage III sarcoidosis.

A previous chest x-ray, done in 1988, was normal with no evidence of sarcoidosis.

The patient denied respiratory symptoms such as cough, shortness of breath or decreased exercise tolerance. Examination of the chest showed bibasilar crackles approximately one-fourth of the way up. Transbronchial and transtracheal biopsies performed in 1999 were consistent with sarcoidosis. The patient was clinically asymptomatic. Initial pulmonary function tests done in July 2000 showed a mild decrease in diffusing capacity that normalized when related to alveolar volume.

The patient had a weight loss of 25 pounds over 8 months with decrease of appetite in August 1999. An esophagogastroduodenoscopy with biopsy performed that same month showed chronic gastritis with no evidence of malignancy. The patient was empirically treated with H2 blockers and was followed in the clinic regularly. Yearly mammograms also showed no evidence of malignancy.

During follow-up the patient did well except for occasional complaints of dyspepsia and vomiting. Additional weight loss of 7 pounds over 3 months was noted in February 2001 and a decision was made to perform other tests to determine the etiology. In June 2001, she developed shortness of breath. Exploratory laparotomy demonstrated massive ascites. Pathology samples did not determine if the source was the colon or the ovary. Due to the advanced stage of malignancy, the patient was treated palliatively. She died in July 2001 at age 81, two years after her sarcoidosis was diagnosed.

INFORMATION FOR AUTHORS

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THEME ISSUE
MEDICINE, MONEY AND MORALS

Rosamond Rhodes and Daniel A. Moros, guest editors

SEP 20 2004

Introduction Rosamond Rhodes and Daniel A. Moros 217

A History of Medical Payments: Continuity or Crisis? David A. Valone 219

Medicine as a Business Merrill Matthews, Jr. 225

Ethics, Economics, and Physician Reimbursement Mary Ann Baily 231

Two Cheers for Physicians' Conflicts of Interest Lance K. Stell 236

Ethics in the Marketing of Medical Services Stephen R. Latham 243

Selling Organs for Transplantation Lewis Burrows 251

Payment for Egg Donation and Surrogacy Bonnie Steinbock 255

Spreading It Around: Money for Researchers and Research Participants Rebecca D. Pentz 266

Panel Discussion 271

GENERAL ARTICLES

Early Reactions to Harvey's Circulation Theory: The Impact on Medicine Steven A. Lubitz 274

Evaluation of Serum Anion Gap in Patients with Liver Cirrhosis of Diverse Etiologies Hatim Hassan, Jung H. Joh, Bruce R. Bacon, and Bahar Bastani 281

Compression of the Radial Branch of the Median Nerve Due to an Anomalous Muscle Belly of the First Lumbrical in a Child Mark E. Pruzansky 285

Letter to the Editor 287

Required Form for Authors C3

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Introduction

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Issues in Medical Ethics:

Mixing Money and Medicine

THE INVENTION OF MONEY by the Lydians sometime between 800 and 650 BCE is hailed as one of the great advances in civilization. Money enables people to exchange whatever they have to offer for the things that they need and desire. Money facilitates transactions and thereby allows individuals to implement their personal values and priorities. By liberating people from the inconveniences of a barter system, money enhanced their ability to express autonomous choice and personal liberty.

Nevertheless, somewhere in its history, money developed a derogatory association; it became "filthy lucre." This negative connotation, related to religious and moral avowals of poverty, introduces a peculiar dilemma into medical practice and medical transactions. Whereas physicians are supposed to altruistically fulfill their fiduciary responsibility by promoting their patients' good, the practice of medicine is, at the same time a livelihood. The Good Samaritan may have only received a reward in heaven, but doctors have always been paid for the use of their knowledge and skill.

This apparent conflict between service and payment, between rendering medical benefits and charging, is the subject of this special issue. The underlying question is whether the bad press and negative associations of money are deserved: Does payment pollute medical service, and does money contaminate medical transactions?

On the one hand, money makes bookkeeping clear and straightforward. It allows people to understand who owes what to whom, and why. Money also makes it easy for people to express their own priorities by paying for the things they value most. And money facilitates distributions and redistributions of goods across and between societies. On the other hand, people do consider some things to be beyond price and inappropriate for buying or selling. They see a sharp line between items and services that can be bought, sold, and exchanged, and other entities for which commodification is inappropriate or impossible, such as the sale of surrogacy services and vital organs. Yet, when medical services can deliver health or happiness, or at least alleviate disease or unhappiness, people start to rethink the boundaries of the permissible and the impermissible.

The first group of articles in this collection addresses the broad theoretical issues of medical services and reimbursement. Historian David Valone presents a panorama of payment for medical services from the time of the Hammurabi Code through to the present. This chronicle of remuneration for medicine allows us to appreciate that today's problems with reconciling the two are not unique to the twenty-first century. Valone's account makes it clear that the tension between ministering to medical needs and receiving compensation has a long history and no simple solution.

The opposing positions are well illustrated by the next four papers. Merrill Matthews, a health policy advisor and architect of health care reimbursement accounts, argues for treating medicine like a business.

The market model, he claims, is now often hailed as the most effective mechanism for delivering high-quality goods to consumers at affordable prices. The market allows patients to decide what is most important to them and provides them, rather than third-party payers, with the wherewithal to get what they want. The market also encourages fiscal responsibility: When patients are insulated from costs, spending runs amok. Matthews explains how health care reimbursement accounts, paired with insurance for catastrophic medical coverage, could provide for medical needs and also engage incentives that encourage efficiency.

Mary Ann Baily is an economist. She explains why the problems of money and medicine are inherently incompatible with a market solution. The general need for medical services, the unpredictability of the need, and individuals' general inability to pay for their medical expenses when they are faced with a catastrophic or significant chronic illness all contribute to making a direct payment system inadequate and unrealistic. Furthermore, the complexity of medical information and the inaccessibility of information about medical expertise, coupled with the emotional stress and urgency involved in medical decisions, make patients far less than ideal consumers in an open market. Baily's argument points toward a solution in a single-payer system that employs salaried medical professionals.

Philosopher/medical ethicist Lance Stell and law professor/medical ethicist Stephen Latham both address the inevitability of medicine's quandary over money. Stell explains the conflict between a physician's medical art and the art of charging and collecting fees. Pointing to Plato's appreciation of the conflict and illuminating an array of conflicts of interest that arise within contemporary medical practice, Stell argues that there is no escape from the dilemma. His solution lies in opening our eyes to these facts and encouraging medicine to minimize the conflicts and learn to manage those that are inescapable. In a similar vein, Latham delineates the major distribution channels for health care and explicates the financial incentives inherent in each. He also explains how access to health care, medical service pricing, promotional tactics, and the referral network all raise problems related to money. Ultimately, he concludes that we must rely upon professionalism and call upon physicians to focus on their moral commitment to the interests of patients, even when the good of patients conflicts with the physician's own good.

The second group of articles takes up the issue of monetary transactions for things that some believe should not be sold. Transplant surgeon Lewis Burrows explains the evolution of his own views on payments to living organ donors. Philosopher Bonnie Steinbock discusses the issues raised by payments for services and gametes in assisted reproduction. Philosopher Rebecca Pentz addresses payments to research subjects. In each of these discussions, one issue is whether payment can be coercive enough to invalidate the seller's consent. Another is whether the degree of risk and harm to the sellers makes the transaction unacceptable. A third issue is whether payments for transplant organs, donor eggs, surrogacy services, or research participation are unacceptable per se. In each kind of transaction it is important to avoid a simplistic and one-dimensional approach, and instead to appreciate the many factors involved and the importance of each in its context.

If we conclude that monetary exchange in these domains could be acceptable, then it is important to understand the conditions and parameters for the ethical conduct of these medical arrangements. The articles in this section further our understanding of the issues that need to be considered and suggest policies and limits for regulating these practices.

In sum, mixing money and medicine may be unavoidable and it may not be entirely bad. Mixing money and medicine does, however, require care and vigilance with respect to the identification of risks and harms that money introduces into medical activities. It also calls for thoughtful deliberation about the complexity of the moral landscape and appreciation of the priorities that people actually endorse in different situations. Many choices that we make every day involve some risk, promise some advantages, and entail some unchosen situational elements. All of these various factors have to be taken into account and the priorities that we assign them have to be justified. In endorsing policies to govern these activities we have to pay attention to honestly respecting the commitments that we endorse (e.g., liberty), to creating incentives that promote the outcomes which we claim to value (e.g., safety), and to policing medical behavior so as to make it easy for committed physicians to uphold standards of medical professionalism.

A History of Medical Payments:

Continuity or Crisis?

David A. Valone, Ph.D.

Abstract

The form and amount of medical payments has been a contentious issue throughout the history of Western medicine. The prices charged by doctors, and the actual payments they receive, have reflected a complex interaction of the social, economic, and political forces impinging upon medical practice. Contemporary concerns about the medical payment system in the U.S. relate, in part, to the unprecedented scale and complexity of the modern system of medical payments. Historical analysis reminds us that medicine and money have always made odd bedfellows. Today's problems may seem intractable, but such problems have been consistent throughout medical history.

Key Words: History of medicine, payment, fees, elite, the poor, direct payments, regulation, Benjamin Rush, competition.

In the history of Western medicine, very few things have remained constant through the ages. Among the few universals one might point to is the following: doctors have always expected to be compensated for their services, just as patients have expected to pay for the care of a doctor. While generalizations across time and culture are often of little value, this consistency in medicine stands in rather striking contrast to the well-documented changes that have occurred in the theory and practice of healing in the West, in the social roles of doctors and other healers, and in the institutional and economic context in which medicine has been practiced. An equally striking fact that one can deduce from such a broad historical sweep is that medical payments have frequently been an issue for doctors and their societies. Such payments have been an issue both for the manner and size of compensation and for their impact on the way in which doctors and patients have related to one another.

Before beginning a consideration of the history of medical payments, we might pause to consider the various types of medical payment that have existed throughout time. These include payments from patients to doctors for a consultation, diagnosis, and recommendations for treatment; payments from patients to doctors, or to others, for medical preparations to treat specific ailments; payments from various corporate bodies such as a city, or from an individual such as a ruler, to a healer as a retainer; payments from doctors to patients as compensation for failed or negligent treatment; payments from individuals seeking medical education; payments to corporate bodies such as hospitals for services; payments to bodies acting as pools of risk for individuals against future medical catastrophes; or lump sum capitation payments from such corporate bodies to individuals or groups of doctors for treating given populations of patients. Each of these forms of payment, further, can involve various third parties, such as insurance companies, fraternal organizations or government agencies. So the problem we face in trying to understand the history of these systems of payment is rather daunting. For the purposes of my discussion, I will focus only on

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the simplest case—direct payments for medical services.

Elite Medicine and Service to the Poor

Of course, this discussion is already skewed somewhat by use of the word "doctor." By using this term we call to mind healers who are part of an elite, and in some form, exclusive medical tradition rather than part of the historically ubiquitous medical panoply of others who offer a variety of services to those in need of healing. If we exclude these lay healers—who more often than not are willing to offer services at a price that meets the market—we can then focus on those for whom the question of medical payments, and the social perception of those payments, is most acute. These elite practitioners (I will henceforth simply call them "doctors") have tended to be particularly cognizant of these issues. Medical writing is full of doctors encouraging their professional colleagues to think about both the manner in which they charge their patients and about how these charges, and the lifestyles they lead to will be perceived among the wider public.

So doctors face a fundamental economic and social dilemma. Since illness strikes rich and poor alike, doctors must necessarily provide services to a wide range of people from varied social and economic positions. Yet doctors, as highly trained specialists with what they perceive to be special knowledge and unique powers, also feel a professional separation from the mass of society. In this way, physicians have to some degree always wanted to be seen, and see themselves, as removed from the great mass of society. This elitism has had both a social and economic dimension to it. In the ancient world, the Greeks were fond of a quotation from Homer that seemed to secure the place of the doctor above others in society. In *The Iliad* (1), when the physician Machaon is wounded in battle he is quickly removed from danger, for "a doctor is worth many men put together, at extracting arrows and applying soothing ointments." Historian Vivian Nutton notes (2) that the Greeks tended to omit the second and more practical half of this couplet, in such a way as to confirm "the doctor's own self-image as a man somehow raised above the majority by his skills." Such a belief, of course, plays somewhat on the dual meaning of the word "worth" in Homer's verse, with its economic as well as social connotations of value. A doctor who is of greater value to society than others can presumably leverage that greater worth into fees commensurate with his social utility.

The degree to which ancient physicians such as Hippocrates set themselves off from society in general and from those of a lower social class in particular is controversial. Little can be said with certainty about the life of that most famous ancient doctor, other than the starkly economic fact that he was willing to teach medicine to anyone who could pay (3). This is particularly ironic in light of the Hippocratic Oath's admonition to teach the healing practice for free, but only to those within the Hippocratic extended family. While we need not be surprised by such tensions in the Hippocratic tradition, which are well known, this particularly sharp contradiction should serve to remind us just how thorny issues of money can be in medical practice.

An especially sensitive issue, not surprisingly, has tended to be the gap between the relative affluence of elite doctors and the financial resources of their patients. While this problem has not been historically universal, since at times even elite doctors have been placed in economically challenging circumstances, it has persisted. Particularly troubling has been the charge that doctors have ignored, or been unwilling to treat, those who are unable to pay their fees. Hebrew doctor Asef Judaeus wrote in the eighth century that the physician should be wary of failing to provide services for the poor (4): "Do not close thy heart to mercy toward the poor and needy," he wrote in his *Admonition*. Judaeus also composed an entire treatise on the treatment of the poor, comprised of remedies that could be procured for nothing. He also had his students swear an oath that bound them to attend to the poor without charge (5). Closer at hand, early American doctor Benjamin Rush was more forthright in his insistence on the treatment of the indigent and on the related topic of the social perception of doctors' fees and their lifestyle. In *The Virtues and Vices of Physicians* (6), he noted with chagrin that "[a]varice in all its forms of meanness, oppression, and cruelty is a frequent vice among physicians." Rush had in mind, no doubt, the denial of services to the poor, but also shows of ostentatious wealth by doctors.

This issue of doctors' treatment of the poor was a particularly sensitive one for Rush. With a practicality reminiscent of his contemporary Philadelphian Benjamin Franklin, he noted that physicians do a particular disservice to themselves and their profession when they deny service to older patients who have fallen on hard times, particularly those who they treated in the past. Such "sordid conduct," Rush asserted, was particularly heinous, since these patients had often been the ones who had first patronized a physician's services and to whom the doctor was therefore in debt for his success. The late-nineteenth-century medical crusader Elizabeth Blackwell was more absolute on this issue (7), noting that physicians must not "enter upon medicine as a trade for getting money." For Blackwell this issue was in many ways at the very heart of medical practice (8), since it was her firm belief that "every branch of medicine involves moral considerations, both as regards the practitioner and the patient. Even the amputation of a limb, the care of a case of fever, the birth of a child, all contain a moral element ... which cannot be neglected without injury to the doctor, the patient, and to society." For Blackwell to extend these moral considerations to money was particularly significant, since it was for her a basic reason why women needed to enter into the medical profession as reformers and moral guardians. Critiquing medicine as too much of a business was one way that Blackwell proposed moving medicine back to what she believed were its true roots: the care and ennobling of humanity. Blackwell's sense was that this represented a job for which women were particularly suited.

Government Regulation of the Medical Marketplace

Given the economic issues related to medical practice and the power that doctors have over their patients' life and death, it is not surprising that this aspect of medicine has often been the target of government control or regulation. Like so much else in medicine, medical payments have often, though by no means universally, been legally regulated. A striking example of this comes in one of the world's most ancient law codes, *The Code of Hammurabi*, which was used to govern the ancient civilization of the Babylonians nearly four thousand years ago. *The Code* contains a number of regulations concerning the rights of doctors to receive specific payments for services they provide, and what could best be described as malpractice protection for patients against failed operations. Significantly, specific payments are set for particular procedures, perhaps the first recorded instance of medical price fixing. Thus, code number 215 requires that "if a physician make[s] a large incision with an operating knife and cure[s] it, or if he open[s] a tumor (over the eye) with an operating knife, and saves the eye, he shall receive ten shekels in money." Correspondingly smaller payments, one-half and one-fifth the above amounts respectively, are required for successfully performing the same procedures on plebeians or on slaves. Similarly, payments for the curing of a disease in "the soft part" of a man or the setting of a broken bone brought payments of five, three, and two shekels for patients of the upper, lower, and slave classes respectively. On the other hand, failed surgeries brought serious consequences for the physician. If an upper class patient died after surgery, or lost an eye in a failed ocular procedure, the physician lost the hand that had done the cutting. Similar failures on lower class or slave patients brought less catastrophic consequences for the doctor: the death of a slave was compensated with the full value of the slave, the loss of a slave's eye imposed on the physician half of the slave's value (8). While such regulations might seem draconian by our standards, they did serve to protect to some degree the interests of doctors as well as patients. Those who entered into the role of healer had a clear sense of both the risks and rewards of their chosen field. Patients could count on a surgeon who had a real stake in their case's outcome, and the barrier to entry for quacks and other charlatans was dauntingly high.

At other times, the regulation of payments to doctors has been less overt. Many periods witnessed neither government oversight of medical practice nor regulation of the medical marketplace. But more often than not, the response of political authorities to the difficulties posed by medical payments lay somewhere in between complete control and total *laissez-faire*. The medieval period is an excellent example in this regard: healers were often kept under the watchful eye of both the secular and ecclesiastical authorities in many areas throughout this period. This was particularly true in the High Middle Ages. During this era the Church moved aggressively to bar members of monastic orders from the practice of medicine, largely because of its economic profitability. The Church's regulations, designed to discourage "temporal gain" among the members of the mendicant sects, demonstrate the degree to which the profit motive underlay practice even in that era (9). Similarly, the medical guilds of the late medieval era had a strongly economic foundation, although they also served as bodies regulating practice and licensure, as well as ensuring competence. By limiting medical practice, though, to those who had their imprimatur, they provided the underpinning for a regulated price structure as well. Of course, these guilds were formed and run by the practitioners themselves, and so were not official governmental bodies. But like all medieval guilds, they were enmeshed in the larger feudal system, their charters generally granted by local authorities, and they were thus ultimately not independent organizations but rather subservient to the local sovereign.

Medical Payments in the U.S. Before the 20th Century

This historical survey of medical payments is not meant to be comprehensive, but rather to provide some perspective on the issue that we are most concerned with, namely the development of the modern American system of medical payments. Medicine in the U.S. has gone through its own peculiar historical development. It began, as typified by the aforementioned early American doctor, Benjamin Rush, as an outgrowth of the medical world of Europe in the early modern period. Like many doctors in the late colonial and early national period, Rush was educated both in the New World and in the Old. He earned his M.D. from the University of Edinburgh in 1768 and helped to establish the first American medical school in Philadelphia soon after. In his autobiography, Rush commented extensively on the development of his practice as a business enterprise. He noted that when he began his practice, he had few of the advantages that would have secured an easy entry into a successful practice in urban and relatively wealthy late-eighteenth-century Philadelphia. These advantages included (10) "the patronage of great men," the "influence of extensive and powerful family connections," and "the influence of a religious sect or political party." Hence, somewhat ironically, Rush concluded that the only means at his disposal for the securing of business was to attend to the medical needs of the poor.

For support in this venture, Rush had several pearls of wisdom. First, he recalled having once read as a boy an autobiography by famed Dutch physician Dr. Hermann Boerhaave, whom he remembered as saying (10) "the poor were his best patients, because God was their paymaster." By this, one can only assume that Boerhaave, and his disciple Rush, saw their reward for medical services to the poor to be part of their spiritual redemption. The other bit of advice was knowledge he had of two other physicians, one in Scotland and the other in England, who had established themselves in the same way. Rush, never one to downplay his own achievements, also noted that attending the poor was in line with his own natural sympathies, which was to react with kindness to every person in distress. For the first several years of his practice, much of his business seems to have been made up of such patients. Rush found success in this path; his business and professional standing were gradually built up over the course of his first decade in Philadelphia, although not without arousing some antipathy among the established doctors of the region. Others apparently objected both to the way that he carried on his practice and to the medical ideas that guided him. Nonetheless, within about five years his practice had grown from almost nothing to an annual income of £900, Pennsylvania currency. While the value of colonial currency was notoriously fluid, this might translate into about £500 sterling, which was certainly a comfortable living in the late eighteenth century.

Rush also provided a kind of summary of the business aspects of his practice during his more than thirty years of work. Overall, Rush estimated that he had never been compensated in any way for approximately twenty percent of his business, either due to explicitly providing services free of charge to the poor or though the nonpayment of bills. Despite the large percentage of service provided without charge for one reason or another, Rush felt little remorse for this unpaid work. Indeed, he emphasized that whenever patients asked for their bills to be reduced or forgiven, he did so without hesitation. And he was proud of the fact that he had provided medical services at no charge to the colonial forces in the Revolutionary War. His one regret was for not being more aggressive in pursuing those who had failed to pay despite being in a financial position to do so. His sorrow was not so much for his lost income, as his feeling of having encouraged such people to ignore their social obligations, and thereby having allowed such individuals to defraud others (10).

Rush's experiences represent those of a successful, and ultimately prominent, urban physician in the late-colonial and early national period. The experience of American doctors in other settings, though, was not as rosy. For those who practiced medicine among the urban poor, or on the less densely populated frontier, the physician's life and business practice could be much less rewarding. One nineteenth-century American doctor, James B. Cranfill, reported the following after beginning his practice in the state of Texas in 1879 (11): "I was enabled to collect the first year of my practice $1500 [sic] either in money or convertible trade. I was not a stickler for details in the matter of collections. I would take anything on a medical bill from watermelons to cord wood, from cabbages to calves. I soon had an assortment of property, and was able, by my natural trading instincts, to make good use of it." Medical practice on the frontier often necessitated such creative business dealings. Currency was scarce, and the trade in precious metals was uncertain at best. Around the same time, in 1877, Dr. Henry F. Hoyt had an unfortunate encounter with one of his first patients, after literally hanging out his shingle in the town of Deadwood in the Dakota Territory. Two years before, gold had been discovered in the Black Hills, bringing thousands of prospectors, and one novice and somewhat naive physician, into the region. Hoyt was quickly taught a lesson in frontier medicine. After traveling ten miles outside of town to see one of his first patients, who had a serious gunshot wound, Hoyt was paid with a considerable pile of gold dust. Upon his return to town, however, he was shocked to be told by that "a good part of [the] dust was phony." Hoyt learned his lesson, though, and henceforth carried with him in his medical saddlebag a bottle of acid to test the validity of his fees (12).

Under these conditions, many doctors in frontier regions attempted to contract out their services in advance. This strategy, when it could be put into effect, had many advantages, chief of which was that the physician could demand prepayment. They also frequently supplemented their income by supplying customers with various medications, generally their own concoctions (13). The difficulties faced by physicians in the business side of their practice were increased by the fact that, during this period, competition among doctors was expected. Such competition came not only from other professionally trained doctors but from an array of "healers" as well. In an era of Social Darwinism, the attitude that unbridled competition was a guarantee that the able would survive and prosper was widespread even among doctors (14). Such competition took its toll on doctors and their wallets. Around the turn of the century, a survey of the incomes of 46,000 doctors revealed that more than one-third earned less than $2,000 per year, and more than half earned less than $3,000. This would have placed the majority of them in the lower-middle to middle classes of society. During this period, however, the average income of the top one percent of doctors was $45,000 (15).

Such extremes in the medical business largely began to level off by the early twentieth century. Thanks in part to restrictions on medical education in the wake of the Flexner Report (16), the business climate for medicine began to change quite dramatically. Still, physicians and physician interests groups like the AMA continued to oppose those they perceived as having a detrimental effect on the business side of medicine. They were openly hostile to a variety of alternative medical practices, such as osteopathy and chiropractic, and to many innovations in systems of medical payments, including group practice and various forms of health insurance (14). By the 1930s, doctors had, for the most part, succeeded in stabilizing the economic conditions they faced by limiting the supply of physicians and convincingly setting themselves apart from other types of healers; this stabilization of the medical market, not surprisingly, came at a price to others. By the early years of the depression, concern had begun to arise about the increasingly high cost of medical care, the poor state of public health regulations and staffing, and the relative scarcity of professional physicians in rural areas. In 1927 a committee chaired by Dr. Ray Lyman Wilbur, with the support of the AMA, commenced work on the problem of the cost of medical care in the United States, with the goal of ensuring that "adequate medical services are to be made available at reasonable costs, to the citizens of this country ten or twenty years hence." While this group made a series of recommendations, their effectiveness at stemming the increasing problems in medical economics was limited (17). The perception of a crisis in medical payments, especially among the poor and in rural areas, continued to increase.

In Cooperstown, New York, a conference convened in the late 1930s to address the growing crisis in rural medical care. Of all the problems faced in the health care situation in rural communities, perhaps the most severe was the lack of doctors, caused in large measure by the extremely poor economic climate faced by rural doctors. At this conference, Lloyd C. Warren, then president of the Otego County Medical Association, spoke about the severe problems encountered by rural doctors. According to his description, rural doctors faced real economic hardship. On the one hand, their fees were necessarily low, since the communities they served were generally fairly poor. On the other hand, they faced considerable expense. They needed to provide their own drugs and supplies, an office from which to practice, and a car, since house calls were common, especially for emergencies. In addition, conscientious doctors would incur expenses for medical journals, books, and professional dues. All of this meant that some 35–40% of a country doctor's gross income was consumed by these various expenses. On top of this, a country doctor's work was really a 24-hour job, since there was no one else to call when medical crises arose (18).

Conclusion

These narratives concerning medical payments in the United States and elsewhere suggest a few consistent, if not universal, tendencies in the way in which the business of medicine has been conducted. First, not surprisingly, it should be clear that the issues that we face now are not unique. Indeed, any perception that we are currently experiencing an unprecedented crisis in medical economics may well be exaggerated. The practice of medicine and the pursuit of profit have always fit together awkwardly, and in many ways the two simply do not work together. Second, as is often the case, the perception that problems that we face today are unprecedented, or particularly severe, does not bear out under historical scrutiny. This is not to deny, of course, that some of the issues that we currently face, such as the sale of organs or cost-saving incentives limiting services to patients, or indeed the scale of today's problems, are different from those in the past. The underlying issues, though, remain largely the same. How can medicine overcome the fundamental gap between the universal need for medical care in a world composed largely of people with limited means, and the need of doctors to be fairly compensated for their skills, time, and years of training? This dilemma may well be fundamental to medicine, and in an era when medicine has become among the biggest of businesses, the difficulties it raises loom larger than ever.

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Medicine as a Business

Merrill Matthews, Jr., Ph.D.

Abstract

There is a growing debate over whether medicine should function like a business, guided, as businesses are, by concerns such as profits and customer satisfaction. Of course, for-profit businesses already permeate medicine, and those businesses are not confused about their priorities: providing high quality goods and services people want, at affordable prices. These companies know that they must do well in order to continue doing good.

Critics of the business model argue that the profit motive makes health care too expensive and that only by nationalizing the health care system can doctors provide high quality care at an affordable cost to society. However, a survey of journals and newspaper articles about the Canadian health care system, often cited as an anti-business model for U.S. reform, reveals that quality has suffered significantly under that system. Patients wait in long lines for health care, and sometimes cannot get help at all.

This paper argues that incentives in the U.S. health care system are complicated, and that health care needs to work more like a business—not less. Doctors don't know whom they are serving—patients, insurers, employers or the government—because it is usually someone other than the patient who is paying the bill. The way to get the incentives structured properly is to allow patients to control more of their health care dollars—perhaps through a system of Medical Savings Accounts. Following the business model is the only way to ensure that medicine provides high quality services at affordable prices—just like every other sector of the economy.

Key Words: Business model, Canada, single payer, rationing, incentives, medical savings accounts, managed care.

Were this country beginning from scratch today, so that we had to consider separately each segment of the economic system and how it should work, many politicians and food policy experts surely would assert: Food is unique. And because it's unique, it could never be part of a free market system where consumers are free to make their own choices and vendors try to maximize profits.

Just consider, critics would assert, some of the problems that would arise if people could profit from the sale of food. We know that food is a necessity; everyone has to have it. Thus, consumers would be at the mercy of food producers, who could charge whatever they wanted to charge. Moreover, because there would be a financial incentive to keep costs as low as possible, food producers would constantly look for ways to cut quality. The result of these two forces would surely mean that consumers would pay very high prices for very low quality. And, of course, since most people aren't trained in nutrition, there would need to be an army of trained nutritionists to help them make good decisions.

Social thinkers helping to organize this new food system would point out that since humans must have food, it should be a basic human right. As a result, people without enough money to pay for their food should nevertheless be allowed to walk into a grocery store and take anything available without paying for it. These planners also might be concerned that under a free market system, higher-income individuals would be able to buy not only more but higher-quality food than those with low incomes, thus creating a two-tiered system. Such a situation, they might argue, is unfair and unjust. Do we really want a country in which some people have steak, while most settle for ground beef?

Their solution: raise taxes and use the increased government revenue to create a national food system that would ensure that everyone has equal access to food. Fortunately, we are not creating a food system from scratch. The one that has served us well for centuries operates almost completely under the free mar-

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ket system, and the result has been that the quality of food is high, the prices are low, and there is more than enough to go around. So why is it that people say that "medicine is unique" and want to do to the health care system what our food policy analysts might have done to the food system?

The Business of Medicine

For the past several years there has been a growing debate among philosophers, ethicists, health care professionals and public policy analysts over whether medicine should function like a business, guided, as businesses are, by such worldly concerns as profits and customer satisfaction (1). Surely, they say, a profession as old, as self-sacrificing and as dedicated to the end of suffering and the betterment of humanity as medicine should be guided by some nobler, more altruistic goal.

Of course, the truth is that business permeates medicine—and big business at that. Health insurance and managed care companies, and the pharmaceutical and medical device industries are irrevocably intertwined with the health care system. Even doctors' practices are businesses; they pay rent, buy equipment, occasionally borrow money, meet payrolls and (usually) close out fiscal years with more income than outgo. Business is as important to medicine as new pharmaceuticals are to an effective physician: You just can't have one without the other. And most of those businesses are not confused about their priorities. They are there to help people, but they know that unless they make a profit, they won't be able to help people for long.

Some doctors, as well as some philosophers, health policy analysts and visionaries, see medicine as a social endeavor. Physicians were meant to heal, not degrade themselves over paying rent, balancing books, fighting off lawsuits, justifying their decisions to managed care companies, or trying to keep Congress from destroying the health care system.

Some physicians think medicine already looks too much like self-serving capitalism. Business is about taking care of yourself; medicine is about taking care of others. Business is guided by pragmatic decisions, medicine by ideals, and some physicians seek to take the business out of medicine so that the ideals can prevail. The idealists hope to do good without regard to doing well; the businesses in medicine strive to do well in order to continue doing good.

I will argue that, in contrast to such idealistic views, the problems facing the health care system result not from its being too businesslike, but because the practice of medicine doesn't act enough like a business. Business is guided by the very pragmatic goal of providing high quality goods and services to people, at affordable prices. Isn't that also the goal of medicine? Even those who think the government should run the health care system believe that. And they usually argue that nationalizing the health care system, thereby minimizing or completely eliminating the business element, will keep health care costs affordable while freeing doctors to provide quality health care. But is that what actually happens when a health care system is nationalized?

Do Single-Payer Systems Provide Quality Health Care?

Countries with national health care systems spend less on health care than does the U.S. For example, in 2001 the U.S. spent 13.9% of its gross domestic product (GDP), on health care, while Canada—a frequently cited "model" for U.S. reform—spent only about 9.7% of its GDP (2). But spending less on health care is not the only—and probably should not be the primary—goal. The challenge is to maintain a high-quality and responsive health care system while spending less money.

Has a country like Canada achieved that goal? The *New York Times* has revealed numerous problems all across Canada. According to one story (3):

- "[I]n Winnipeg, 'hallway medicine' has become so routine that hallway stretcher locations have permanent numbers. Patients recuperate more slowly in the drafty, noisy hallways, doctors report."

- At Vancouver General Hospital on the West Coast, "Maureen Whyte, a hospital vice president, estimates that 20 percent of heart attack patients who should have treatment within 15 minutes now wait an hour or more."

- Finally, "Last summer [i.e., in 1999], as waiting lists for chemotherapy treatments for breast and prostate cancer stretched to four months, Montreal doctors started to send patients 45 minutes down the highway to Champlain Valley Physicians' Hospital in Plattsburgh, New York."

As the *New York Times* points out, "Canada has moved informally to a two-tier, public-private system. Although private practice is limited to dentists and veterinarians, 90 percent of Canadians live within 100 miles of the United States, and many people are crossing the border for private care" (3).

Case Study: A Flu Epidemic

A recent flu epidemic in Toronto expanded the waiting times to see a family physician to 5–6 weeks. Appointments were scheduled so far into the future that most patients would have recovered from their illness and would no longer have needed to see a doctor.

Unfortunately, many patients who needed to see a doctor immediately didn't even have an emergency room option. In December of 1999 and January of 2000, Toronto emergency rooms were so full that they were turning away patients—regardless of how sick they were. According to a story in the *Toronto Star*, 24 of 25 emergency rooms were closed on Monday, December 27, 1999. By the next day, "21 of 25 emergency wards were refusing to accept any new patients, no matter how ill or critically injured they might have been, or were accepting only the most serious cases" (4). According to the authors, "Toronto Ambulance's paramedics were working the phones like veteran travel agents, trying to find emergency room spots for their patients on a day when the demand was close to its peak." Only three weeks later, an 18-year-old boy, Joshua Fleuelling, died of asthma because the emergency rooms were on "critical care bypass" and couldn't accept him (5).

Case Study: Waiting Lines

But it gets worse. In March of 2000, Canadian Health Minister Allan Rock told the House of Commons, "There are people who are waiting too long, waiting hours in the emergency ward, waiting months for referral to a specialist, waiting a year for a long-term bed, waiting what seems to be an eternity for someone to answer the call button in an understaffed hospital" (6). Rock is referring to the Canadian health care system—one in which, according to supporters, accessibility, efficiency and affordability are all supposed to converge.

Canadians often wait weeks and even months to see a specialist. According to the Vancouver, British Columbia-based Fraser Institute's annual survey of waiting times in Canada (7):

- The average total waiting time between referral from a general practitioner and treatment by a specialist rose from 13.3 weeks in 1998 to 14 weeks in 1999.

- Waiting times between specialist consultation and treatment (which does not include the time between seeing a general practitioner and getting to see a specialist) increased from 7.3 weeks in 1998 to 8.4 weeks in 1999.

- Waiting times for diagnostic tests also underwent some increases. For example, the median wait for a CT scan across Canada was five weeks in 1999, a 6.4% increase over 1998.

Case Study: Canada's Budget Debate

In 2000, Canada's health care system reached a crisis over funding. In this case, however, the crisis wasn't instigated by budget deficits, but by a budget surplus. Some Members of Parliament wanted to pass an income tax cut of at least 20%, which others opposed, claiming that the proposed budget only offered two cents in health care funding for every dollar in tax cuts (6).

Ralph Klein, premier of Alberta, who wants to bring a little of the "business mindset" back into Canadian medicine by letting for-profit clinics perform some of the procedures currently provided by Canadian hospitals, has offered one solution to the problem of waiting lines. The government health care program, known as Medicare, would reimburse the clinics for the care (8).

Case Study: Limited Access to Technology

In a system where health care budgets are tight, bureaucrats and politicians tend to see new technology as too costly to justify the benefit they would provide. As a result, funds, if any, are provided only for the purchase of a limited amount of the newest technology. The decisions on what to buy and when to buy it are often arbitrary and guided more by good politics than good medicine.

Even more important, these arbitrary limits usually enshrine the medical knowledge and techniques current at a particular point in time. A central control system cannot afford new medical discoveries and treatments, because they aren't in the budget and no funding or other resources is allocated for them. Thus, a single-payer system inherently tends to foster outdated medical techniques and resist new or innovative ones.

Although single-payer proponents cite Canada as a system that rivals the U.S. in the availability of new technology, the country lags behind many of the Organization for Economic Cooperation and Development (OECD) countries. While Canada ranks fifth in terms of total health care spending (as a percent of GDP), a recent study by the Fraser Institute, comparing OECD data, found that the country (9):

- Ranks 21 out of 28 in CT scanner availability;
- Is 19th out of 22 in lithotriptor availability;
- Is 19th out of 27 for the availability or MRIs.

Stories abound of Canadians going to extreme measures in order to gain access to medical technology. For example, several years ago an enterprising hospital in Guelph, Ontario, decided to allow animals needing computed tomography (CT) scans to enter the hospital in the middle of the night—charging pet owners C$300 apiece. There is nothing necessarily wrong with that action, except that thousands of people in Ontario were waiting up to three months for an appointment on the same machine (10).

"I'd go any time," said Greg Moulton, who was in the middle of a two-month wait to learn why he was having "excruciating" headaches (10). Because people are not allowed to pay out of pocket for medical procedures covered under the government-run plan, they have to wait. However, if you're a dog, you can get medical technology immediately.

When dogs get better treatment than people, then people will "become dogs." In December 1999, the *Washington Post* reported that waiting lines for magnetic resonance imaging (MRIs) in Ontario had grown so long that one Ontario resident "booked himself into a private veterinary clinic that happened to have one of the machines, listing himself as 'Fido'" (11).

Case Study: Rationing

At a 1999 conference in England organized by the Institute for Public Policy Research, Alan Milburn, health secretary of England, said of the country's National Health Service (NHS), "The NHS—just like every other health system in the world, public or private—has never, or will never, provide all the care it might theoretically be possible to provide.... So within our expanding health system there will always be choices to be made about the care to be provided" (12).

Thus the question is, "Who decides about who gets what?" In a single-payer system, the government makes the larger decisions about funding levels, leaving the doctors, hospitals and other health care providers to make the tougher individual decisions about whose care to limit. The targets of rationing are usually the marginal cases, and that often means the very young, the very old and the very sick. The patient is often simply told, "There's nothing more we can do for you," a statement that is true within the confines of the budget. The range of medical options is simply not discussed in these circumstances.

The *Canadian Medical Association Journal* (CMAJ) reported in May 1999 that during a 12-month period, 121 patients waiting for coronary bypass surgery were removed from the waiting list because their conditions had deteriorated to the point where they were unlikely to survive surgery. "In Quebec," according to Steven Pearlstein of *The Washington Post*, they've sent more than 250 cancer patients over the border to the United States this year (1999) to get treatment and still there are 350 who have waited more than four weeks for radiation or chemotherapy (waiting more than 4 weeks is considered medically risky)" (11). Such stories are not rarities, but commonplace, even in the best of single-payer systems, and Canada is one of the best. The fact is that health care rationing is pervasive when the government controls health care. And as health care costs rise and government budgets tighten, rationing expands.

Canada has been very explicit about its attempt to avoid using the business model in health care. And this has led to waiting lines, increased pain and suffering, needless deaths, lack of access to technology and rationing. Is this really the model the U.S. should follow for providing quality health care?

The Need to Get Incentives Right

The primary problem with the doctor-patient relationship as it exists today is that the incentives are complicated. In a market system, providers of goods and services know who they are trying to please—the customer—and why. It is in the interest of those who provide goods or services to make sure that their clients and customers are satisfied. A restaurant owner has an interest in making sure that those who come to his establishment enjoy their dinning experience. An attorney has an interest in ensuring that her clients are satisfied with her services.

This is not simply about economic interests. Most vendors want to have a good reputation for producing and selling quality products. They want people to respect them for what they do and how they do it, not just for how much they make. Fortunately, those who develop a reputation for quality products or services usually get rewarded financially as well. When incentives are operating properly, everyone walks away from a transaction happy—the vendor because he sold a product or service and made some money, and the customer because she has a product she wanted for a price she was willing to pay.

But who is the doctor trying to please? The patient or the managed care company or the employer? Most professionals have a fiduciary responsibility to their clients to work for their best interests. But to whom does the doctor owe a fiduciary responsibility? Since the patient gets the care but the insurer pays the bill, it isn't clear exactly who the client/customer is.

The current medical system distorts all of the normal incentives. Doctors do not believe that they are serving patients, but rather the insurers, the employers, the government or the managed care companies that are paying the patients' bills. These managed care companies strive to disenroll those physicians who provide too much care. Patients aren't satisfied, because they feel that somebody is keeping them from getting the care they were promised and their employer paid for. And employers, insurers, state and federal governments, and managed care companies aren't happy, because they believe that doctors and patients are driving up health care spending and finding ways to sidestep or minimize the controls meant to keep health care costs low.

Consider just one of the perverse incentives common in the system. Under most circumstances, workers get paid more for doing more. But under a managed care capitation system, doctors get paid more for doing less. There is no way that this kind of incentive system will encourage satisfaction and confidence from either the patient or the physician.

Making Medicine Work More Like a Business

The problems facing the health care system are not going to be resolved unless it begins to operate more like a business. That means getting the incentives right once again. The reason businesses seek to offer a quality product at an affordable price is that customers want value for their money. That is, they weigh cost, quality, service, convenience and other factors before making a decision on what to purchase.

To a large extent, customers in the health care system—otherwise known as patients—don't seek value for their dollars, because in the vast majority of cases they are spending someone else's money (i.e., the insurer's, the managed care company's, the employer's or the government's).

This insulation from the cost of health care has created a number of problems. When people are insulated from the cost of their economic decisions, they will spend more than they otherwise would. And the medical establishment has exacerbated the problem by pushing for everyone to be covered for everything. That is a prescription for financial disaster.

In addition, the tax system provides a generous tax break to those who get their health insurance through their employer, but not to those who buy it themselves (13). Because most employees think that employer money spent on health insurance comes from the employer—although most economists believe it is actually paid for by the employee because it is part of the total compensation package—they want their employer to buy as comprehensive a policy as possible. That practice has also contributed to the problem of people being overinsured.

If people were to reduce some of that cost insulation—say, by choosing a high-deductible health insurance policy that covers them for a major accident or illness—they would begin to act more like consumers act in every other segment of the economy (14). If they were allowed to put the resulting savings in a tax-free account to pay for health care, they would be getting the same tax advantage they currently receive when the employer pays the health insurance bill. In fact, that is what flexible spending accounts (FSAs) and medical savings accounts (MSAs) are meant to do, but both plans are currently burdened by restrictions that have reduced their appeal (15).

Although it may seem radical, there is nothing new about this idea. Fifty years ago, health insurance was reserved almost exclusively for catastrophic medical events (13). It was even called "major medical." When patients visited a doctor, or the doctor came to their house, they paid those costs out of pocket. Of course, some patients didn't have the money and doctors had to work something out with them, perhaps by accepting a reduced fee or even nothing at all (16). The medical community's drive to make sure everyone has comprehensive health insurance has not resolved that problem. Doctors still have to reduce their prices, only now it's the managed care companies that are demanding the discounts.

Just imagine how much different the office visit would be if patients had to pay the full cost of, say, Celebrex or Vioxx out of their own funds or an MSA. Most would be much more interested than they are today in getting the doctor's opinion about whether the name brand or a less-expensive, over-the-counter pain reliever would do. That is where value would come in. Once patients are concerned about value, and health care providers are concerned about ensuring that patients receive that value, the proper incentives will be in place—and the health care system will begin to look a lot more like a successful business (17).

Conclusion

There is no escaping it: someone will determine who gets what in health care. The question is whether that someone will be the patient in consultation with a doctor or some company overseeing health care costs.

For years many people both inside and outside the medical community have argued that "medicine is unique." And because it is unique, neither doctors nor patients should have to weigh the costs of health care with the benefits. As a result, managed care companies, employers, insurers and the government have stepped in and weighed those costs and made those decisions.

The medical profession will probably never operate completely like a business. Health insurance—even with a high deductible—will continue to insulate people from the full cost of care. And doctors will continue to provide care even to those who cannot afford it. But medicine can learn from business, and even become more like it. That means adjusting the incentives so that they create a positive, rather than a negative, impact.

In becoming more business oriented, medicine doesn't have to give up its own unique values. Indeed, it is only by adopting the business model that medicine can embrace its values in providing a high level of quality for an affordable price—just as the food system and most other businesses do.

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Ethics, Economics, and Physician Reimbursement

MARY ANN BAILY, PH.D.

Abstract

There has been much debate among health care professionals over how physicians should be paid for their services. This paper addresses the topic through an economic and ethical analysis. It starts from the premise that fairness and cost effectiveness should be the goals of a good physician reimbursement system. Using the goals of fairness and cost effectiveness as measures, it examines the current market model. Finding that the current model provides neither fairness nor cost effectiveness, the paper compares the structure of the physician services market to the assumptions made by economists in the idealized market model. Two major imperfections are found in the former. These imperfections are an asymmetry in information between patient and physician, and the uneven and unpredictable distribution of health needs. These two imperfections are examined in light of the goals set out in the beginning of the paper. The paper finds that, given the imperfections, physician reimbursement as it currently exists is incompatible with the goals of fairness and cost effectiveness. In conclusion, several recommendations are made, most significantly a broadening of the interpretation of physician agency, i.e., physician as "agent," and the switch from a fee-for-service physician payment system to a salaried medical practice.

Key Words: Medical economics, medical markets, imperfect information, need, medical ethics, fee-for-service, reimbursement, physician-patient relationship, insurance, salaried practice.

ANOTHER PAPER IN THIS COLLECTION provides a historical description of how physicians have been paid (1). In contrast, this paper discusses how they should be paid, based on the perspectives of economics and ethics (2–6).

The Goals: Equity and Cost Effectiveness

If you asked the question "What is a physician payment system supposed to accomplish?" I think most people would say that we want the "right" amounts and quality levels of physician services produced and delivered to the "right" people, we want physicians to get a "fair" reward for their efforts, and we prefer not to sacrifice any more than is necessary of other goods and services in order to achieve this. In other words, the goal is a payment system that is both fair and cost effective.

Economic Perspective: The Market Model

When economists think about getting goods and services allocated efficiently, they think immediately of markets. The market is a core concept in economics; it is the model of buyer-seller interaction that determines what is produced and how it is distributed through the so-called law of supply and demand. The key to a market's operation is the price, which adjusts to bring the amounts of a good people are willing to sell into harmony with the amounts people want to buy.

Economists devote much of their time to analyzing market behavior. This is appropriate in an economic system like ours, in which most goods are allocated through a system of interconnected markets. Such analysis is a very useful tool for explaining where existing patterns of production and distribution come from and how they will change in response to various changes in the factors that determined them. But to economists, the analysis is useful for more than explanation and prediction. They use it to draw normative conclusions—to argue that markets are a desirable form of economic organization. When the market price harmonizes de-

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cisions to buy a good with decisions to sell, it harmonizes the preferences of consumers with societal resources. Economists can show that under certain idealized assumptions, a market system yields an efficient composition and distribution of output without heavy-handed central planning or control. Theoretically, each good is produced with the minimum sacrifice of other goods, because the competitive process creates desirable incentives for both producers and consumers, so that when they pursue their individual self-interest, they also serve the common good.

But what about fairness? Does the market system get goods to the "right" people and give them a "fair" reward for their contribution to society? It depends on how you define "fairness"—but in fact, a case for the fairness of the market outcome can be made. When price rises to eliminate excess demand for a good, those who value the good most get it. When individual incomes are determined by markets for labor and other productive resources, those who contribute valued resources to society reap the rewards.

But this argument only goes so far. The trouble is that in a system based on market exchange, people who have nothing to put in get nothing out—and the initial distribution of productive resources (personal characteristics like strength and intelligence as well as ownership of land and natural resources) is heavily influenced by history and pure luck. Therefore, even in a market system that works perfectly, most people would support intervention to ensure that people with limited initial resources would have enough income to afford basic necessities. And of course, the assumptions are idealized—no real market is perfect.

Nevertheless, for many economists, the vision of the ideal, plus the perception that real markets often do perform the resource allocation task reasonably well, creates a preference for the use of markets. When a market doesn't yield the desired results, they tend to want to "fix" the market rather than abandon it altogether. For example, if some people lack basic necessities, they would rather redistribute income than control the prices of the needed goods or give the goods as handouts—they would rather get a fairer distribution of purchasing power and let people buy what they want.

So why not let a market allocate physician services and, in the process, determine what physicians earn? Physicians market their services to consumers and each service has its price; the result is called the fee-for-service reimbursement system. However, I think it's fair to say that, as a society, many have not liked the results.

Problems with the Market Outcome

Briefly, the results have been neither cost effective nor fair. I am not going to spell this out in detail here, since you already know the story—how we spend an enormous amount on health care yet have the nagging feeling that we are not getting our money's worth—how some people get too little care, while others get too much (7–11). Instead, I am going to focus on the role physician reimbursement plays in bringing about these undesirable results, and offer some alternative thoughts about reimbursement structures that might lead to better results.

To understand the effects of reimbursement, an economist automatically begins by looking at the structure of the physician services market and asking how it matches up with the assumptions of the idealized model. In fact, there are many imperfections in this market. The two that are generally considered most important are the asymmetry in information between patient and physician, and the uneven and unpredictable distribution of health needs.

Imperfect Information

The basic market model assumes that buyers have complete information about the product they are buying and the benefits it will give them. This is a simplification that works fairly well for most goods; however, it does not work well for health services. To decide how much benefit will result from a purchase of physician services, a person must typically rely on the advice of the very person who will supply them. In other words, physicians act as agents, helping patients determine what to buy, and they can influence the demand for health care by the advice they give. If physicians only do what their patients would do if the patients fully understood medicine, the agency factor does not change the outcome. But do they? In fact, should they? What is the health care agent's duty—to the patient, to the rest of society, to the physician himself—and what should be done if these duties conflict?

Ethical Duties of Physicians

Many ethical questions currently troubling physicians are related to the question of the proper nature of agency. Historically, most physicians have believed that it is their ethical duty as a patient's agent to do everything medically beneficial for that patient without regard to cost. Of course, the patient has to pay the cost. A patient who cannot afford the care a physician believes is beneficial raises a difficult dilemma. If the patient is already in the physician's care, duty requires that the care be provided anyway. Therefore, to avoid financial disaster, physicians have to manage their practices so that they do not take on too many patients who will not be able to pay, taking refuge in the belief that their ethical duty extends only to those patients for whom they have accepted initial responsibility.

This view of agency is quite different from the economist's view. Economists (and some physicians) are more inclined to see agency as a contractual relationship in which the physician undertakes to serve the patient's interest as the patient defines it. After all, even if a patient can find the money, the medical benefits it buys may not compensate for the sacrifices which become necessary in other areas of life. In this view, a physician should consider cost to the extent that it matters to the patient (of course making sure the patient fully understands the tradeoffs between medical benefits and costs).

These two positions differ with respect to the meaning of serving a patient's interests. They are united, however, in ignoring the interests of others. The physician does so on the grounds that to do otherwise is unethical; the economist on the grounds that it is unnecessary. Why unnecessary? Because in the (idealized) market system, efficiency is served by decentralization, and equity is promoted, if necessary, through policies implemented at other levels of the system, through taxes and transfers of purchasing power.

Uneven and Unpredictable Distribution of Needs

Let us turn to the other important special feature of this market. Neither the medical ethics nor the economics position on agency deals adequately with the complications associated with variability in health care needs. A person's demand for health care depends on health status, which in turn depends on chance. Few people have enough money to ensure access to all the important medical care they might ever need. The market response is health insurance, which people can buy to protect themselves against the financial consequences of changes in health status.

Once a person is insured, however, price no longer plays its key role as mediator between consumer preferences and resource costs to society. Consumers do not weigh the marginal benefit of health care against the price, because they do not pay the price. Of course, indirectly they do pay, because premiums must cover the expenditures on behalf of all those insured, but there is no incentive to consider this, since any one person's consumption is only a small part of the whole.

A system of extensive health insurance in which physicians are paid on a fee-for-service basis greatly eases ethical conflicts. The more physicians do for patients, the more they are paid, while the insurance coverage shields patients from the full financial consequences. In such a system, the difference between the two concepts of agency blurs. Physicians are protected from worry about adverse financial effects of clinical decisions, on themselves or the rest of society, as long as they minimize involvement with the uninsured and those on public programs that pay below-market fees.

Cost Effectiveness Implications

Unfortunately, in the real world, neither patient nor doctor cares about the relationship between benefits and costs. When the doctor is paid on a fee-for-service basis and the patient is well insured, both are happy to use medical care until the point where further care would yield no benefits at all, rather than to stop at a point where benefits are commensurate with costs. Thus, many people are getting care that is not worth what it costs. Under these conditions, there is also little pressure on suppliers to produce efficiently. In a competitive market, the pressure of competition makes producers stay efficient. If they do not, they are "competed" out of business.

When a market organization has no price system or some functional substitute for it, costs and insurance premiums rise, pricing some people out of the market, even as the well-insured receive a pattern of care that fails to match benefits with costs. This is a serious problem.

What to do? First, it is important to reach a new consensus on the nature of the physician's agency role. In a world of third-party payment, an economist ought to argue that the concept of agency must be understood in a broader sense. A narrow definition of self-interest seems to lead a patient to prefer a doctor whose clinical decisions ignore all costs that do not fall directly on the patient. Yet the patient is part of an insurance risk pool, which in the aggregate bears the costs of all care received by the members. It is in the patient's long-term interests to agree to limits on utilization that reflect an evaluation of the relative benefits and costs of treatments. This holds down the cost of membership in the risk pool and ensures that the common resources are not squandered on low- or zero-benefit care. It also makes it less likely that the patient himself will be priced out of the risk pool.

Similarly, the medical ethics interpretation of the physician's agency role must be broadened. The view that the physician's ethical duty is to be strictly a patient advocate without regard to cost or consequences for others seems too narrow, given this interconnected dependence people have for the resources to meet their health care needs.

These are arguments based on cost effectiveness considerations. The point is, unless this interconnectedness is taken into account by physicians, we will spend too much for the advantages of pooling risk. The arguments would be valid even if there weren't any differences in purchasing power that made it difficult for some people to afford insurance, and there weren't any differences in initial health status that made insurers reluctant to offer affordable insurance to those considered poor risks.

Equity Implications

When fairness is also considered, the arguments for a broader interpretation of agency have even greater force. A more generous income redistribution policy would help to improve access to health care, but it would not solve the problem entirely, given the limited ability of private insurance markets to pool the risks resulting from genetic health endowments and chronic illness. Moreover, society seems to have a special sense of moral obligation concerning access to an adequate level of health care, one that is independent of its overall concern about fairness in the distribution of generalized purchasing power. Given this, a system that gets benefits in line with costs will also make tax dollars go further in the provision of health care to fulfill this societal obligation.

Remedies

In sum, information asymmetries, the need for risk-pooling, and the special redistributive importance of medical care mean that we cannot rely on a decentralized market process to produce an efficient and equitable allocation of health care at the individual patient level. Other mechanisms must be found to do what prices do in simpler markets. Some people have focused on bringing financial incentives back into the patient's decisions to use care, by introducing more cost-sharing at the point of use. This is a dead end. Cost-sharing cannot go very far without losing the whole point of insurance, i.e., freedom from the worry of unexpected, large medical bills. Moreover, since patients still have to rely on their physicians for advice about the benefits of care, physicians must inevitably retain a central role in their decision-making. The health care system must somehow guide doctors to practice cost-conscious medicine—cost-conscious in the sense that patients get neither too much nor too little in either quantity or quality of care.

There has been some movement toward this view of the physician's ethical duty toward patients, but the process has been agonizingly slow and confusing. Meanwhile, market forces have been fueling very rapid changes in the structure of physician reimbursement, changes that have taken a form that I personally find troubling. As public and private payers have responded to growing pressure to control health care expenditures, they have increasingly relied on the imposition of direct and indirect financial incentives to physicians to reduce costs. At the same time, physicians are receiving no clear guidance from society as to what the proper balance between too much and too little should be.

I think it is impossible to achieve the goal of a cost-conscious but fair standard of care purely by means of financial incentives to physicians; moreover, it is ethically dubious to try. Making clinical decisions on the basis of personal financial gain is considered unethical by both economists and ethicists, under both the narrow interpretation of agency that focuses on the short-term interest of the individual patient and the broader interpretation that also takes account of the individual patient's long-term interests and the mutual dependence of all the members of the health care system. If financial incentives have any role at all, it can only be in combination with clear ethical principles and explicit guidance.

Society must find a middle ground between two extremes, pejoratively described as expecting physicians to practice cost-benefit analysis at the bedside or, alternatively, to practice cookbook medicine out of government cookbooks.

Finding the right way will require a cooperative endeavor in which standards of cost-conscious practice are set by the medical profession and public and private third-party payers working together in the public interest, through consensus development, technology assessment, quality improvement, and quality assurance activities.

I think this cooperation would be easier to achieve in a structure in which individual physicians do not gain or lose directly from decisions about how care should be limited. Instead of manipulating financial incentives in ever more complex ways to induce physicians to alter their use of resources, we should consider replacing fee-for-service physician reimbursement with salaried medical practice. In our economy, most people who work for organizations are paid on a salaried basis, not by piecework. Their performance is judged on the basis of general performance standards, and they are fired, promoted, and given merit raises and bonuses in accord with the quality of their work. With the evolution of medical technology, more and more physicians are practicing medicine as members of organizations, rather than as individual solo practitioners. Why shouldn't such a payment structure work for physicians? The change might be initially unpopular, as organized medicine has traditionally resisted salaried practice. However, if the change made it easier to achieve general cooperation in clarifying the standard of care to be provided to patients, there could be a significant reduction in the uncertainty and ethical discomfort physicians experience as they make clinical decisions.

Conclusion

Recently, there have been calls for a new medical ethics—one in which the focus of ethical obligations shifts from individuals to populations. This rhetoric implies that physicians must recognize a separate, new obligation to serve the interests of society—an obligation that is in direct conflict with their traditional obligation to do what is best for the individual patient. I think this rhetoric is misleading, and I want to dissociate myself from it. Rather, the obligation to cooperate in defining and implementing a cost-conscious standard of care is an integral part of the physician's obligation to serve the interests of the individual patient, when those interests are less narrowly conceived. The sooner patients and physicians realize this, the sooner we will be able to address the difficult task of reforming our health care system to be both more efficient and more fair.

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Two Cheers for Physicians' Conflicts of Interest

Lance K. Stell, Ph.D.

Abstract

This paper will attempt to demonstrate that conflict of interest is an unavoidable feature of medical practice, medical institutions, medical publications, and medical research. It also seeks to show how and why current regulations are ineffective in curbing fraud and abuse. The paper goes on to argue that, in light of the incentives incorporated into current reimbursement arrangements, physicians have to learn how to manage the conflicts they face and remain true to their fiduciary responsibility to patients.

Key Words: Conflict of interest, physician-patients relationship, fiduciary responsibility, fees, bias, professional journals, trust, HIPAA.

"...no one of his own free will chooses to...take other people's troubles in hand to straighten them out, but everyone expects pay for that...."
Plato (1)

A medical license invests the physician with social recognition, authorizing him to present himself to the public as a competent, trustworthy guardian of patients' health interests. When someone becomes a license-holder's patient, ideally, she welcomes rather than fears the physician's broad discretion to act in her best interests. This means that the physician must attend to her complaints, outline to her his findings and their significance, and define care options and their expected consequences. If his best medical judgment is that an illness is self-limiting or will respond adequately to self-care, it is his duty to say so. If she requires treatment, he may offer it. On the other hand, if his best medical judgment is that her condition requires referral to a specialist or subspecialist for further diagnostic work-up or treatment, he must say so.

At every juncture from presenting complaint, to work-up, to care plan, to treatment, to discharge, the physician's guardianship of the patient's health interests permits benefit to the patient, but also to the physician, to the hospital, to professional colleagues, pharmaceutical and device makers, and society, very often at third party payer's or society's expense. It is no exaggeration to say that "Every physician-patient encounter is a conflict of interest. Every physician-payer encounter is also a conflict of interest" (2).

It doesn't follow, of course, that all conflicts of interest between physician and patient are equally important. Some conflicts of interest are "more equal," more problematic, than others.

Conflict of Interest: Psychological Roots and Ethical Dynamics

Plato may have been the first thinker to provide a systematic analysis of the physician-patient relationship that explains why conflicts of interest are an ineluctable feature of it. The account goes as follows:

Despite the fact that the physician presents to the public as a practitioner of the medical arts, there is "an additional art" which is not

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professed, namely, the art of fee-charging and fee-collecting. Since the art of medicine enables the physician to diagnose and treat disease, its practice primarily benefits the patient, not the physician. However, Plato notes that "no one of his own free will chooses to...take other people's troubles in hand to straighten them out, but everyone expects pay for that" (1). It follows that the physician would not willingly attempt to help solve the patient's problems were it not for his practicing the additional art that benefitted him, namely, the fee-charging, fee-collecting art.

The physician's practice of the two arts results in mutual benefit. However, distinguishing these arts analytically and separating them in practice are not the same. How should the physician sequence the practice of these arts in time? For example, may the physician practice the money-making art "prior to" establishing a physician-patient relationship, e.g., by his assessing the ill person's "ability and willingness to pay" (a.k.a., the "wallet-biopsy")? After all, the money-making art remedies any reluctance the physician would otherwise have about attending to the ill. Yet this seems unfair to the ill person, because, depending on the circumstances of her illness and her access to alternative providers, she would be susceptible to extortion. On the other hand, if the physician's practice of the fee-charging/collecting art must be delayed until the patient has recovered, her gratitude may be insufficient to motivate her to pay her bill.

Plato ignores these problems, but he insists that the physician must not practice both arts simultaneously. Once the physician-patient relationship is established, and when treating the patient, the physician must give priority to the medical art, which by definition advantages the patient, not the physician. Otherwise, the physician becomes a fraud, because by giving priority to his unprofessed art he becomes a "mere moneymaker." In other words, what makes it non-fraudulent for the physician to profess medicine while also practicing but not professing money-making, is his perfect adherence to the fiduciary principle: "No physician, insofar as he is a physician, considers his own good in what he prescribes, but the good of the patient; for the true physician is...not a mere moneymaker" (1).

Obviously, "true physician" is not a description of any real-life person, but rather an abstract, ideal physician who is making a medical decision for his one and only patient. Insofar as this ideal physician has other patients, they are abstracted away, so neither he nor we consider the time-tradeoffs in caring for more than one patient. He serves his patient tirelessly. He considers only one thing when applying the medical art to the patient's situation—the patient's good—and nothing else. The true physician's single-mindedness reflects his perfectly just, well-ordered soul. His self-control renders him nonsusceptible to all incentives that bid to motivate his rendering less or more treatment than the medical art directs. In particular, financial incentives cannot motivate the true physician to undertreat or to overtreat or to otherwise influence his medical judgment.

All human physicians fall short of Plato's ideal, "true physician." Human physicians have many patients and suffer from chronic time-management problems. They lack perfect self-control. The prospect of reimbursement may well influence their medical judgment to some degree, resulting in overtreatment or undertreatment rather than "right treatment."

Implications of the Incentive Principle

If "pay," whether denominated in financial or in nonfinancial terms, tips the balance of motivation between a physician's being "unwilling" to his being "willing" to "take [the patient's] troubles in hand to straighten them out" (presumably, a good result of incentives) then it is reasonable to expect that "amount" and "kind" of compensation will exert recurrent influence on the physician's motivation and judgment, making a difference between the physician's being "grudgingly willing to attend," "reluctantly willing to attend," and "eagerly willing to attend, at all times" (a more troublesome result).

- The promise of fee-for-service (FFS) reimbursement at customary and reasonable rates creates a well-appreciated incentive for the physician to accept and serve as many FFS-sponsored patients as possible. Less obviously, it creates an incentive for the physician to avoid subspecialist referral. The aggressive utilization-bias created by FFS reimbursement does not necessarily benefit patients sponsored by it. One study of well-insured cancer patients found that they received worse care and more dangerous treatments than uninsured patients (3).

- The bias against referral created by FFS also creates an incentive for subspecialists to pay primary care physicians for referrals. Although fee-splitting is regarded as unethical in the U.S., it is widely practiced in Japan, where subspecialists pay up to $2,500 (U.S. equivalent) per referral.

- Fee-splitting is an economic corrective for the primary care physician's incentive to treat beyond his capability. Prohibiting fee-splitting advantages primary care physicians as a group. It disadvantages subspecialists and patients who might have benefitted from referral or who might have avoided iatrogenesis associated with primary care physicians treating beyond their ability.

- The incentive to overtreat FFS-sponsored patients advantages the physician's self-pay and nonpaying patients by enabling cross-subsidization of their care. The ability to cost-shift marginally effects the physician's willingness to attend to self-paying and nonpaying patients. It may also cause the physician to overestimate how much *pro bono* care he provides.

- Steadily declining Medicare reimbursement to physicians will reduce physicians' willingness to care for Medicare-sponsored patients (4). The effect will be marginal, not categorical. Rather than causing the wholesale discharge of Medicare patients from a physician's practice, declining reimbursement will tend to influence his willingness to accept the next Medicare-sponsored patient into his practice. As the number of Medicare-sponsored patients in a physician's practice decreases, his increasing reluctance to accept new Medicare patients will affect most persons not yet Medicare eligible, including those of his current patients who are now otherwise-sponsored.

- Since the medical standard of care is defined by reference to what the average member of the profession in a particular community does in particular circumstances, and since financial reimbursement exerts influence on the medical judgment of the average member of the profession, medical indications for a procedure may be influenced (more or less) by the prevailing reimbursement scheme. For example, cataract surgery is performed on approximately 1.4 million patients per year. The procedure accounts for Medicare's largest expenditure, and is performed at lower rates in pre-paid settings than in fee-for-service settings. It follows that whether cataract surgery is medically indicated varies somewhat with reimbursement models (5). Another example: Physicians tend to avoid screening for and diagnosing substance abuse disorders, because they rarely receive reimbursement for treating it. To the extent that society relies on the medical profession's diagnostic data to estimate the incidence of substance abuse, it will underestimate the incidence of substance abuse (6).

- As a rule, Medicare does not pay for patient-administered prescription drugs. However, it will reimburse hospitals for intravenous (IV) prescription drugs administered to Medicare beneficiaries. Medicare will also reimburse physicians for the IV prescription drugs they administer to outpatients. Both hospitals and oncologists obtain cancer drugs directly from pharmaceutical companies at wholesale prices. As a result, both hospitals and oncologist have an incentive to favor IV administration of medications over "patient administration" whenever there is a choice. Indeed, it is hard to justify keeping a patient in the hospital if she does not have at least one IV line. However, when a physician orders IV chemotherapy for an inpatient, nurses administer the drugs which the hospital has procured. The hospital rather than the physician bills Medicare for the drugs at retail prices. On the other hand, the oncologist may bill Medicare at retail prices for the cancer drugs he has obtained wholesale, provided that he infuses them in an outpatient setting. Obviously, as inpatient care reimburses less well, outpatient oncology becomes more attractive. Making outpatient cancer care more attractive to oncologists may be welcomed by patients but not by hospitals. Hospitals have an incentive to call attention to the Medicare "loophole" that allows physicians to bill at retail prices for prescription drugs they administer by IV to outpatients. Furthermore, the social interest in adverse-event monitoring and peer review are more difficult to manage in an outpatient setting.

Medical Ethics, Made (Too) Simple

Perhaps disillusioned by the scope and depth of physicians' self-interest (7) and the overall commercialization of medicine (8), one state medical board has announced an absolutist corrective: "zero tolerance" for physicians' conflicts of interest:

> ...patients...come to the physician in a vulnerable condition, believing that the physician has knowledge and skill that will be used for their benefit. Patient trust is fundamental to the relationship thus established. It requires that...there be no conflict of interest between the patient and the physician or third parties. (9)

Norman Levinsky has weighed in similarly (10): "Physicians are required to do everything that they believe may benefit each patient without regard to costs, or other societal considerations.... It is society, not the individual practitioner, that must make the decision to limit the availability of effective but expensive types of medical care."

Unfortunately, as Plato's 2500-year-old analysis makes plain, "zero-tolerance" for physicians' conflicts of interest is equivalent to "zero-tolerance for physicians."

Levinsky's idealistic-sounding nostrum for ethically challenged doctors, "You must do whatever benefits the patient..." rationalizes the physician's "doing everything" when expectable patient benefit is small or speculative, but also when expectable physician benefit is much larger and more certain, not to mention outsized financial gains accruing to his hospital, or to medical supply companies, pharmaceutical companies and device makers. Rather than reminding physicians that declining marginal benefit for patients should not provide ethical cover for ignoring the obvious incentive effects of comparatively larger gains for themselves, Levinsky would make physicians' willful ignorance of their disproportionate gains into a virtue rather than a vice.

Conflicts of Interest in the Nonprofit Sector?

In 1991, Genentech, a for-profit biotechnology industry leader, contributed $2.5 million to the American Heart Association (AHA, a private, nonprofit corporation) for construction of its national headquarters in Dallas, Texas. In the mid-1990s, the AHA launched a health care initiative to reduce morbidity and mortality secondary to "brain attack," its campaign term for acute ischemic stroke. The AHA touted the promising results of a clinical trial of a new bioengineered fibrinolytic agent, tissue plasminogen activator (tPA). The AHA estimated that tPA might save as many as 400,000 lives per year, reduce stroke-related morbidity, and perhaps even reverse paralysis secondary to stroke. During the 1990s, Genentech's contributions to the AHA exceeded $11 million. Genentech's support was not disinterested: it had developed and patented tPA and intended to market it. In 1996, the FDA approved tPA (Alterplase) for use in ischemic stroke. The expert panel that issued the favorable recommendation (eight to one) contained only one member not known in advance to favor tPA approval. His professional history was uniquely devoid of ties to Genentech. By contrast, six of the eight supporting panel members had financial ties to Genentech, four of the eight supporting experts were members of Genentech's paid-speakers bureau, and two of the eight had received research support from Genentech (11).

The American Heart Association never published the dissenter's opinion, which pointed out that the AHA's initial enthusiasm for tPA was based on only one trial, and that a statistical analysis of that trial's results showed that chance alone could explain the "finding" of tPA's apparent efficacy.

Subsequently, no fibrinolytic trial demonstrated that tPA confers a mortality benefit in treatment of acute ischemic stroke. On the other hand, several studies found an association between tPA and increased mortality. More worrisome, one fifth of patients initially diagnosed with stroke by expert teams were found subsequently not to have suffered stroke. And patients falsely diagnosed "positive" for stroke who receive tPA emergently are exposed to risk unbalanced by benefit (12).

Nevertheless, in August of 2000, the AHA upgraded its recommendation for tPA from "optional" (class II b) to "definitely recommended" (class I). Having won FDA approval and treatment-guideline support from the AHA, Genentech has no interest in funding a comparative efficacy study matching tPA against streptokinase (a very cheap, generic fibrinolytic agent). One of its scientists explained, "We don't know how another trial would turn out. And if we don't come out ahead, we would have a [tremendous] self-inflicted wound" (13).

Clinical trials sponsored by drug companies are much more likely to report positive results than trials that have nonprofit sponsors. Does this suggest that physicians who conduct drug-company-sponsored clinical trials have a conflict of interest which increases the likelihood of their producing positive results for a fee? Perhaps.

However, it is estimated that drug development costs resulting in FDA approval average $500 million per drug (14). If so, wouldn't a drug company have an obvious incentive to use adverse selection to withhold from clinical trials any drug/device antecedently regarded as unlikely to win approval?

Similarly, suppose that nonindustry funding sources are comparatively indifferent as to whether otherwise rigorously designed study proposals might yield negative results. Wouldn't it be likely *a priori* that more of its sponsored studies would fail to find benefit or would be equivocal?

Also, nonfinancial conflicts of interest may distort judgment as much as or more than financially based conflicts. An interest in winning desirable academic appointments, in securing tenure and promotion, in publishing articles in prestigious journals, in vindicating one's pet theories, sheer animus, etc., may bias judgment just as powerfully as funding from an interested party.

Seeking Unbiased Professional Judgment: The Professional Journals

Professional journals are imperfect bias filters. They may eliminate some biases, but also add some of their own.

The professional credentials that qualify an editor or reviewer to evaluate a manuscript submitted for publication also make it more likely that he or she will have conflicts of interest with its authors. Review-process opacity renders readers unable to discern whether publication decisions may have been marginally influenced by shared mentorship, favor-repayment, political loyalty, frank envy, or even retaliation against professional rivals or a study's sponsors. Editors with their own record of professional achievement vary in their susceptibility to think less well of a manuscript that ignores their own or friends' contributions to the field or treats such contributions dismissively, without "due respect."

Drummond Rennie, a longtime medical journal editor himself and a sturdy critic of the medical literature's quality, has written (15):

> "...there seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print."

Conclusion

It follows from Plato's analysis of fiduciary relationships that incentives sufficiently strong to forge them also present a hazard to them. If perfect adherence to the fiduciary principle as modeled by the "true physician" is used as a standard, then every trust-bearing agent, including all real-world physicians, must be continually out of compliance, more or less.

Conflict-of-interest management is an exercise in practical, "second-best ethics." The problem is that we have no consensus about "an acceptable rate of noncompliance." Flagrant abuses of trust that come to public notice invite speculation that similar cases are going undetected. The speculators are not necessarily disinterested either.

Thomas Hobbes's "state of nature" argument proved that trust and anxiety are inversely related. Where there is no basis for trust whatsoever, there is no rational limit on our anxiety, and we can never invest too much in precautionary measures. Once there is a rational basis for social trust (provided by some type of social contract), public anxiety declines and the perceived need for precautionary measures goes down. Still, should social trust decrease for some reason, social anxiety would increase and the public's willingness, collectively and individually, to invest in precautionary measures would go up. Declining social trust in the medical profession, therefore, has fueled a growth market in precautionary measures, especially in regulation and enforcement. The Health Insurance Portability and Accountability Act (HIPAA) is the latest example.

This federal law criminalizes any "scheme or artifice" to defraud, or obtain money by false pretenses from any health plan (federal or otherwise). The prohibitions are sweeping in their scope. For example:

- Federal law is violated if even one purpose (as opposed to a primary or sole purpose) of a payment, whether received or given, is in exchange for or to induce the referral of patients or the ordering, purchasing, or recommending of items or services. It "may" be a defense that the improper purpose was "incidental," "minor," or "not material" (16).

- Although courts recognize that some benefits received or given by providers may be *de minimis*, any payment or other benefit may violate the law when the amount is sufficient to influence the physician's reason or judgment (17).
- The fact that a fee charged is reasonable will not serve as a defense if the intent underlying the arrangement that generated it can be shown to be an exchange of payment for referrals (18).
- There need not be proof of an agreement to make referrals, or to order, purchase, or recommend medical items or services. Intent may be inferred from the circumstances of the case (19).
- The mere potential for increased charges to, or a payment to be made by, a federal health care program may be sufficient for the law to be violated; no actual payment is necessary as long as the challenged charge for an item or service might be reimbursed by a federal health care program (20).
- The fact that an arrangement is "common" in the health care industry is not a defense to a kickback violation (21).

These prohibitions are so sweeping that virtually every financial relationship in the health care industry potentially violates federal law. The magnitude of threatened penalties, despite the unlikelihood of their imposition on any one of the million health care providers in the United States, creates an incentive for each of them to invest in precautionary measures to reduce the hazard of federal prosecution. The resulting redistribution of resources does nothing to improve care quality, nothing to reduce the incidence of medical errors, nothing to improve access to health care.

On the contrary, to guide the redistribution of resources, the federal government encourages providers to adopt "voluntary compliance programs" and to self-disclose improper billing. Law firms have opened new sections of their practices to market precautions to their client-providers. No "money-back guarantee" accompanies these products. There are at least two competing trade associations that credential HIPAA compliance officers. Hospitals may now purchase insurance against the consequences of filing false claims—an irony, since a predicate of insurance is uncontrollability of risk.

It might be argued that these anti-kickback and anti-fraud provisions effectively offset physician and other provider incentives to take unfair advantage of their trust, and that as a result, providers will become more trustworthy. But if the number of law enforcement actions are an index to provider trustworthiness, the trend looks bad. For the past 6 years, civil, criminal and administrative fraud enforcement has logged an increasing number of cases.

It has been repeatedly asserted that 10% of health care spending ($1.15 billion in 1998) is lost to fraud, waste and abuse. Since this percentage has not been revised in more than a decade, aggregate losses from "fraud and abuse" must be growing inexorably with increases in health care spending. Indeed, the sweepingly broad definition given to unlawful provider conduct implies that the only restraint on the number of enforcement actions is the size of the enforcement budget.

Plato claimed that a society's rate of increasing injustice correlated with its number of lawyers. More lawyers create more regulations and proliferate causes of action, leading to citizens spending more and more of their time in litigation. Incentives create relationships. One cheer. Conflicts of interest create occasions for regulatory oversight. Two cheers?

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Ethics in the Marketing of Medical Services

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Abstract

This paper deals with the ethics of marketing medical services by physicians, medical groups, hospitals and other mainstream medical caregivers in the United States. It does not deal with pharmaceutical marketing, since that raises a number of special issues, some of them legal and some having to do with the unique culture of pharmaceutical marketing, which really ought to be dealt with separately. Nor does it touch on the little-explored field of marketing alternative and complementary medicine. It begins with a general description of what is included in "the marketing process." It then briefly tours some of the difficulties faced by those who would market medical services ethically, and ends with some comments on the relevance of professionalism to ethical marketing.

Key Words: Professionalism, medical marketing, market competition, health care, product, placement, price, promotion, ethics.

Marketing 101: The Four P's

MOST OF US ARE APT TO ASSOCIATE the idea of "marketing" with promotion and advertising. But in fact, "promotion" is only one of the famous "four P's of marketing" taught in most business schools.

The first step in any marketing plan is to determine the nature of the *Product* (or service) one wishes to sell. Next, one determines its *Placement*, the distribution channels through which the product or service can best be made available to the consumer. Then, one attempts to determine the *Price* at which the product or service will be both profitable to the seller and attractive to the target consumer—e.g., should this be sold cheaply, as a "loss-leader," or at a steep markup as a luxury item? Finally, one plans the *Promotion*—where and how to advertise. Each of the four P's raises its own characteristic set of ethical questions. *Product* raises questions about product safety and efficacy; *Placement*, about the use and abuse of power within distribution channels; *Price*, about fair pricing, consumer access to goods and services, and the relationship of price to quality; and *Promotion*, about honesty, deception and exploitation in advertising and sales.

Product

There is cause for profound concern about certain "products"—the medical services—that mainstream medical caregivers sell. In spite of the writings of David Eddy (1) and Archie Cochrane (2) on evidence-based medicine, and decades after John Wennberg's initial demonstrations of small-area variations in medical practice (3), many medical services are still not adequately based on science. The first step in medicine's ethical marketing plan must be to continue and expand upon the current efforts to determine which medical services truly are effective. It is surely an ethics violation to sell a service, under false pretenses, to patients who would be better off without it.

On the other hand, there are a number of recent innovations in the "product" area that seem to be morally unproblematic and may even enhance the efficiency and efficacy of medical

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service provision. These involve bundling—or unbundling—of medical services. Hospitals and physicians have bundled services through physician-hospital organizations, in order to deliver more efficiently integrated packages of medical services to insurers and those whom they insure. Some physicians have formed large multi-specialty groups for the same reason. And other physicians have formed disease- or specialty-specific group practices, both in order to deliver their services more efficiently and in order to foster patient disease-management groups. In the last decade, hospitals have also been "unbundling" services that have traditionally been part of general inpatient care, and spinning them off into lower-cost entities (such as ambulatory surgical centers) or specialty hospitals.

The impetus for much of this bundling and unbundling has been economic; these innovations are designed to maximize payment and minimize costs associated with contracting for and delivering various services. But there can be genuine efficiency and quality gains from service-bundling. Specialty groups can gain experience and expertise, and provide coverage with relative ease. Physician-hospital organizations and multi-specialty practices can make intra-group referrals and consultations easy, and they can minimize the transaction costs of contracting with payors and patients. These are real gains.

Placement

Placement refers to the "distribution channel" aspect of marketing: By what avenues will consumers gain access to the product or service? A certain amount of medical service placement is done by medical caregivers themselves, as when, for example, an urban hospital decides to set up a suburban outpost for the convenience of its patients, or when a physician group opens a walk-in clinic at the mall. But in the United States, the primary mechanisms of placement in health care are those tied to insurance coverage. Patients gain access to medical services through a number of distinct pathways dictated by the nature of their insurance coverage (4). The primary distinction here is between those who obtain their health care through private insurance and those who obtain it through government programs. There are subdivisions within each of these basic categories—and then there are the uninsured. This section gives a brief overview of the main distribution channels for health care, drawn largely from the work of James Robinson (4); it then explores the two major kinds of ethics problems connected with marketing through these distribution channels.

Among the insured, self-employed individuals and employees of small firms commonly seek health services through Blue Cross and Blue Shield (BCBS). To attract their wide variety of small customers, BCBS needs broad networks of physicians, health care institutions and allied health professionals, and substantial contacts with the insurance brokers through whom smaller insureds obtain their policies. BCBS also needs to supply brokers with marketing materials about the coverage they offer, and has to work with them to support existing contracts.

Larger employers sometimes use BCBS, but more often they insure their employees through indemnity plans, or use insurers to administer self-insured plans. (Public employees and unions, by contrast, often contract with HMOs.) Large single buyers have the purchasing power to create more exclusive, less diverse networks of health care providers, as well as the power to offer their employees quite limited network choices. This gives them the opportunity to make demands of providers regarding quality of care and to cost-control. (By contrast, BCBS can make fewer such demands, because their priority is on maintaining a large, open network for their diverse small-customer base.) Large employers also have no need of broker contacts, since their contracting and claim-servicing are conducted by in-house personnel departments.

The major distribution channel for medical services is Medicare. There is comparatively less need for marketing within the fee-for-service part of Medicare, since everyone over 65 is covered and almost all hospitals and physicians (at least among the relevant specialties) take Medicare patients. (There is room here, however, for promotion efforts to attract seniors to particular Medicare physicians; these are discussed below.) Such Medicare HMOs as can survive the relatively low governmental compensation rates compete with one another by offering extra services, especially to seniors who lack private Medigap insurance. Medicare HMOs market their services directly to seniors, through senior centers or in personal sessions.

State Medicaid and State Children's Health Insurance Programs (SCHIP) services are woefully ill-marketed. Perhaps because reimbursement is so low and costs to state budgets so high, very little is done to draw eligible recipients into the benefits channel. Neither state Medicaid programs nor SCHIPs have succeeded in enrolling all the adults and children who are eligible for those programs. This leaves over a third of the poor uninsured (5).

The four major distribution channels for health care, then, are: small-group and individual insurance, dominated by brokers; large employer insurance, dominated by personnel departments; Medicare, where limited competition for placement takes place mostly in small meetings; and Medicaid, where special outreach programs enlist—or fail to enlist—eligible patients (4). These distribution channels raise two major kinds of ethics problems, problems of agency and problems of access.

Agents are generally obligated to act in the interests of their principals. Agency problems arise whenever an agent has personal interests that are not well-aligned with his principals', and which therefore threaten to lead him to act contrary to his obligation. In the above schema of health care distribution channels, the principals are the health insurance consumers. Brokers are their customers' agents for the purchase of health insurance, but they also have interests that run counter to their customers' interests. For example, brokers are interested in making a sale even if the products they sell do not fit well with the customer's needs, and they want to maintain a good reputation and relationship with large insurers even when those insurers treat customers badly, and so on.

The large-employer distribution channel has the most difficult-to-manage agency problems. Employers in this scheme serve as their employees' agents for the purchase of health care coverage and the selection of health care professionals. Often, however, employers' and employees' interests are only imperfectly aligned. In theory, employers should have every reason to desire high-quality health care for their employees. Such care reduces absenteeism, increases employee satisfaction, enhances recruiting ability, and reduces the amount of time spent by the personnel department in managing complaints. Similarly, employees should have strong interest in cost-control, since they would prefer to minimize the total percentage of their salary/benefits package that is earmarked exclusively for health care coverage—coverage for which they may not have much use. Nonetheless (perhaps because employees have personal experience relating to quality of care, while employers have better information about firmwide health care costs), employers often end up placing more emphasis on a provider's record of cost-control than on its quality, its communications skills, or its convenience for employees. In addition, in-house personnel departments have an interest in resolving problems swiftly and in using their employees' time efficiently. This can sometimes run counter to their obligation, as agent to pursue employees' claims disputes vigorously. Finally, employers have an interest in minimizing the transactions costs of shopping and contracting, and this may conflict with the interest of employees in transferring from a health plan with which they are dissatisfied.

There is no general solution to such agency-related ethics problems. These problems may be limited by the introduction of financial incentives to keep agents' interests aligned with principals', of monitoring and oversight measures to catch instances when agents act badly, and of bonding by agents to assure their fidelity to principals' interests. But the crucial factor here must be the agent's moral commitment to pursuing the interests of the principal even when it conflicts with his own.

Access issues are, of course, raised most dramatically in connection with the uninsured, who remain outside all of the main distribution channels for medical care. The broad social-justice problems of non-coverage are beyond the scope of this paper, but it is certainly appropriate to note here the ethical failure of marketing in the Medicaid/SCHIP channel. There has been widespread failure at the state level to engage in sufficient outreach, so that the eligible poor actually enroll in publicly supported programs. This has real health costs for those who remain uninsured. It also has long-term political costs, since it contributes to a misunderstanding of the finances of public health care and helps present a falsely reassuring picture of the availability of publicly funded health insurance to the poor.

Price

The ethics of pricing in the market for medical services are decidedly complex. In thinking about medical service pricing, we must begin by noting that a very large proportion of all medical services supplied in the United States are supplied at prices that are set politically, through the Medicare and Medicaid programs. Over the last decade, competing spending priorities, revenue shortages, and the desire to force adoption of better cost-control measures have all led governmental programs to place sharp limits on payment for medical services. The American Hospital Association notes that about 57% of hospitals lose money on Medicare inpatient services (6); the American Medical Association, using data drawn from government sources, estimates that physicians' Medicare reimbursement rates have slipped 14% against their costs of supplying services since 1991 (7). Such limited reimbursement is in fact to be expected from government programs. Given their very large market share, their budgetary interests are best served if, on average, they pay health care providers just enough to cover their fixed costs and overhead, but not enough to cover their full costs of providing services. Pricing at this level should assure that providers continue to take program patients (since seeing program patients, and covering only fixed costs, is less expensive than seeing no patients and covering none), but will also keep program costs to a minimum. This reimbursement scheme creates an instant fairness problem, since the shortfall on program patients has to be made up in the price set for non-program patients.

Most non-program patients are insured, either by their employers or by health insurance companies. Prices for the medical services they buy are commonly set by the market, in negotiations between insurers and health care providers, and between insurers and insureds. The intensity of price negotiation, and therefore of price competition between providers seeking contracts, has undoubtedly risen over the last several decades, first with the cost-cutting pressures of the 1980s and again with the managed care revolution of the mid-1990s. Though fierce price competition is normally considered beneficial for consumers, since it assures that goods and services are delivered to consumers at something close to their cost of production, there are a number of important grounds for worrying about possible ill effects of price competition in the health care sphere.

Here it is worth recalling that, until the early1980s, physicians' and hospitals' ethics rules imposed strong limits on advertising, and on price competition in particular (8). Advertising was widely considered degrading to the profession of medicine, and price-advertising was considered downright dangerous. (Similar norms obtained for the practice of law.) The application of federal antitrust laws to the medical profession abolished many of the formal ethics rules relating to price advertising (8), but a strong social norm against such advertising lives on. The cynical view of this history is that we are well rid of those so-called "ethical standards," since they were not based on ethics at all, but were rather a means of creating a cartel by limiting competition and facilitating price-fixing among medical service providers. But there is a non-cynical argument to be made in favor of such ethical restrictions. Let us turn from history to theory.

It is probably true that few of us really know whether the medical services we have received are of high or low quality. We can be more or less satisfied with a medical outcome, but we cannot dependably convert our satisfaction into a sound judgment about the quality of the service we received. Excellent care can result in poor outcomes, given our mortal nature and the unpredictability of illness. Poor care can result in fine outcomes, given the resilience of the body and the self-limiting nature of much disease. If high-quality care costs more to provide, and if quality is difficult or impossible for consumers to detect, then fierce price competition should have the tendency to drive out high-quality care. Neither insurers or insureds will be willing to pay extra for "quality" that they cannot observe.

Another important problem with price competition in health care is that, as a matter of social policy, we seem not to want what effective price competition normally gives us, namely, a wide range of quality available at different prices. Part of the function of price, in a competitive market, is to signal quality. We expect that $15 watches will not work as well, or last as long, as $200 watches. Yet we are happy to have both kinds of watches on the market. We are not, it would seem, similarly happy with the idea of having low-cost, low-quality health care available in the market, side by side with high-cost, high-quality health care. (There is no doubt that we do have such a cost/quality scale in our current medical system, but public and critical sentiment runs, for the most part, against it.) Fierce price competition drives down the margins of health care service provision, and one use of those margins, historically, has been to cross-subsidize medical care for the poor, allowing even those who cannot afford its actual cost to receive something approximating the highest quality care.

A final difficulty with price-competition in health care is that pervasive governmental and private health insurance virtually guarantees that prices are set at one or more removes from the actual patients who, in consultation with their doctors, make the final decisions about which health care services to buy. Patients are seldom aware of the cost of the services they purchase, and neither in the public nor in the (tax-subsidized) employer-insurance systems do patients bear, via their premiums, the entire cost of their medical risks, let alone the entire cost of their actual purchases. The virtue of the market-competition mechanism is supposed to be that it allocates social resources to those who value them most. But price competition that takes place only in narrow portions of a market otherwise pervasively distorted by tax subsidy, lack of information, political price-setting, and the economics of insurance, cannot be delivering on that promise.

These three reasons (the threat of price competition to quality in markets where quality is difficult to perceive, the tendency of price competition to create multiple tiers of quality, and the inefficacy of isolated price competition in otherwise distorted markets) offer theoretical support for a professional reluctance to embrace price-competition. The difficulty here is that, at least for the privately insured portion of the health care market, price competition is favored by American public policy. Neither hospitals nor physicians can avoid it.

Promotion

We turn, finally, to Promotion. The single most striking fact about advertising for medical services is that there seems to be very little of it. This is particularly surprising, given our evident willingness to spend a great deal on such services. It stands in marked contrast to the wealth of advertising for medical products (especially patented drugs), and for health-related products, from "nutriceuticals" to ab-flattening machines. Not surprisingly, the medical services which seem to attract the most advertising are elective procedures: hair transplants, liposuction, plastic surgery, laser surgery for vision. On one level, the reason for this is obvious. Demand for fuller lips can be created by advertising, while only cancer can create demand for oncological services. But, given the near-inevitability of serious illness for each of us, and the dependably high prevalence of at least certain kinds of illness in the population, one must still marvel at the paucity of advertising for medical services. The only explanation for it, I think, lies with continuing professional norms against advertising directly to patients (about which, more later).

Of course, a great deal of promotion takes place out of the public eye, between businesses within the health care system: group practices and hospitals promote themselves to insurers, health plans promote themselves to employers, and so on.

The business ethicist David Holley has argued that a sale, to be mutually beneficial to buyer and seller, must be based on a purchase decision that is well-informed, unforced and rational (9). Promotional tactics that interfere with any of these three decision-conditions are unethical. Thus, advertisements that are untruthful or deceptive are unethical because they induce consumers to make poorly informed decisions. Threats and the abuse of unequal bargaining power are unethical when they force people into purchases they do not want. And it is of course unethical to sell anything to someone who temporarily or permanently lacks the capacity for rational judgment.

(I note in passing the strong resemblance of Holley's "conditions for uncompelled exchange" to the Catholic moral tradition's description of human acts—those for which we are morally responsible. Human acts are those that are voluntary, knowing and free (10). A purchase by one temporarily incapacitated by grief would be involuntary; a forced sale would be unfree; a sale based on deception would be unknowing.)

In most cases of the "business-to-business" promotional activity briefly mentioned above, the ethical analysis will be straightforward. Following Holley, we may state that all such promotional efforts are ethical if they are truthful and non-deceptive, if they are not coercive, and if they are targeted at persons with full capacity.

Advertising becomes slightly more problematic when it is aimed directly at the proposed consumer of medical services. Here we face greater risks. Individual patients or their family members may need to make decisions about medical purchases when their capacity has been diminished by shock or fear or depression. Marketing tactics that take advantage of this vulnerability are clearly unethical. Patients may be subject to unethical coercion by providers who abuse their position of power, or by payors who force them to accept one treatment option over another. Yet, though these ethical dangers are real, the more analytically complex problems have to do not with rationality or coercion, but with information and the patient's state of knowledge.

At the level of institutional advertising for medical services, we need to consider the distinction between untruthful advertising and deceptive advertising—for an advertisement may be both entirely truthful and deceptive. Particularly in the health care arena, where accurate measures of quality are hard to come by, it turns out to be surprisingly difficult to say anything true, concrete and specific about the quality of care supplied by any given provider that is not also in some way deceptive. A provider can easily engage in stock "puffery"—"We deliver high-quality care at a reasonable price." But the difficulty arises when it attempts to recite actual facts to back that puffery. "We have the lowest death rate of any hospital in the city"—true, but deceptive, since the higher death rates may belong to more sophisticated hospitals that attract more intractable cases. "We conduct the finest cancer research of any facility in the world"—true, but deceptive, unless research somehow translates into quality of bedside care. "Our physicians are all board certified specialists"—true but arguably deceptive, since most listeners do not know what board certification involves, and board certification is in any case no guarantee of quality of care, bedside manner, and so on. The sheer complexity of medicine, and of the quality measures it has available, virtually guarantees that any statement about quality that can fit comfortably in a popular advertising format will be deceptive, because it can only be a partial truth.

In general, it is much harder to become an informed purchaser of medical services than it is to become an informed purchaser of a peach, an automobile, or even a house. Most of us are not frequent purchasers of serious medical services. Except in the case of elective procedures, there is commonly very little time in which to explore our options. There are few *Consumer-Reports*-like sources of unbiased, useful information about medical services. In many cases, we simply feel too ill to spend much energy on comparison shopping or information gathering. Any marketing behavior that takes advantage of this common lack of information, any pressure toward more remunerative treatment options, for example, is unethical.

The traditional solution to this problem of patient knowledge has been for the patient to depend upon a physician as his or her agent for the purchase of medical services. In the paradigm case, the primary care physician examines the patient and then makes a recommendation about what kinds of further medical care the patient ought to purchase. The recommendation may be for additional care or examination by the primary care physician himself, or for specialty care, or for a prescription drug, or for an inpatient stay. The patient relies upon her physician to make purchasing decisions in her best interests, thus cutting out much of the need for advertising to inform patients about available medical services.

This system creates obvious conflicts of interest. Because the physician is the patient's purchasing agent for services that the physician may, himself, profit from selling, he has a personal financial interest in recommending purchases that the patient does not really need. Alternatively, he may recommend services that will not profit him, but that will profit others whom he has an independent interest in pleasing: partners in a practice group, specialist friends, institutions with which he has a long-term affiliation. Some of these conflicts are alleviated by such devices as the second opinion, utilization review, regulations prohibiting physician referrals to facilities in which the physician has financial interests, and regulations prohibiting payments or kickbacks for referrals. But some of these conflicts may be more intractable.

Professionalism: The Fifth P of Medical Marketing?

Medical marketing, then, is full of ethical pitfalls. There are ethics problems with the nature of the medical *product*; fairness and quality problems with the nature of *pricing*; agency and access problems with *placement*; and problems involving deception, lack of information and conflict-of-interest in *promotion*. Where can medicine turn for solutions to these pervasive problems? I believe, perhaps too idealistically, that medical *professionalism* can help—indeed, that *professionalism* should be the fifth P of medical marketing.

What is medical professionalism? As I have already described one version of the doctrine of medical professionalism in this journal and elsewhere (11, 12), I shall offer only a brief summary here. Importantly, the doctrine of professionalism is aspirational; it is a normative description of what medical professionals' motives ought to be, and of how they ought to act, rather than a positive description of how they or their professional institutions have in fact acted in the past. To say that physicians may have occasionally acted badly in the past is thus not to deny the truth of the doctrine of professionalism, but to accuse physicians of having sometimes failed to live up to it.

In short, medical professionals mediate between society and their individual patients, helping on the one hand to restore the sick to social usefulness and dignity, and on the other to advocate for individuals against social norms that are sometimes intolerant of illness. To sustain this mediating function between individuals and society, medical professionals must cultivate a particular set of motivations. The medical professional is motivated primarily not by the desire for wealth or power, but by the desire for public respect and trust, and for a reputation among his or her peers for excellence. (Wealth-motivation could lead to the "capture" of professionals by wealthy private interests; power-motivation could lead to their capture by society through politics; either of these would pull them from their proper mediating function.) The institutions of professionalism (schools, societies, publications, medical staffs, codes of ethics, etc.) are designed to cultivate and reinforce the appropriate motivations. They offer professionals venues in which to pursue, display and celebrate their learning and skills, and to reaffirm their values, both before one another and before the public whose trust and respect they seek to earn.

How might the fifth P address some of the problems of medical marketing? First, with regard to *product*, norms of professionalism can encourage the scientific improvement of medical services, and spur experimentation with different bundles of services; professional institutions should disseminate such improvements and celebrate the researchers who develop them. With regard to *price*, professionalism can serve to counter some of the pressures created by price competition. A professional who is primarily motivated by the desire for excellence rather than by the desire for wealth can (at some personal cost, and within limits set by economic realities) deliver high-quality care even when the price charged does not reflect that quality, and even when the buyer cannot detect it. Similarly, a strong professional ethic can minimize the tendency of price-competition to create different quality levels.

With regard to *placement*, medical professionalism can encourage the provision of free care to those outside the existing distribution channels. A successful professional association—one that has gained the public's trust and respect by being associated with excellence and professional values rather than with pocketbook issues or political struggles—could also engage in meaningful lobbying to improve the public's health, both through increased access to health care and by other means. Finally, with regard to *promotion*, a professionalism concerned with earning the public's trust would limit the use of deceptive-though-true advertising, and would, moreover, minimize the degree to which physicians take advantage of their patients in conflict-of-interest situations.

There are those who will dismiss this idea of "professionalism as the fifth P" as hopelessly naive and unrealistic, but such naysayers actually do not have a very persuasive set of arguments on their side. They can point to the many instances in which physicians, hospitals, and professional associations have failed to live up to the professional ideal, and have been manifestly motivated by greed or by the desire for political power—but that is an argument for reinvigorating professionalism, not for dismissing it. They may dismiss any number of professionals' laudable acts as mere superficial bids for respect or reputation—but such dismissal forgets the deeper truth that the surest way to gain respect is to earn it, and that the safest way to build a reputation for excellence is to be excellent. They may deny that professional institutions could ever affect the motivations and actions of persons so deeply as to counter the human desire for money and power—but here they replace the wisdom and experience of institutional conservatism with a simplistic economism.

Medical services need to be marketed. But they need to be marketed in a way that does not deliver unnecessary or harmful care; that does not leave people vulnerable because of their lack of medical information; that does not contribute to the unfairness in distribution of health care services; that does not sacrifice quality of care to the competitive fray. An ethic of professionalism can help.

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Selling Organs for Transplantation

Lewis Burrows, M.D.

Abstract

The need for transplant organs has far outstripped the supply of available cadaveric organs. Hundreds of people on waiting lists, who could be saved by transplantation, die each year. This severe shortage has justified the extension of transplantation to the use of living donors, but there are still not enough organs to meet the need. This paper discusses the justification for changing policies in order to encourage organ donation. It presents reasons for allowing payments to be made to families that donate cadaveric organs. It also presents reasons for allowing payments to be made to living donors, and guidelines for how an ideal policy could be structured.

Key Words: Selling, payment, organs, transplant, financial remuneration, presumed consent, altruism, ethics.

LIVING DONOR ORGAN TRANSPLANTATION is the only field of medicine in which two individuals are intimately involved: the donor and the recipient. It is also the only field of medicine in which altruistic giving of oneself is the basis of the medical practice. I have been asked to address a very specific aspect of this process, that is, living organ donation for financial remuneration. No other subject in the transplant experience is as controversial. Many of those involved in the field—surgeons, physicians, social scientists, ethicists, and theologians—have expressed an opinion on this issue.

As a result of impressive gains in this field, organ recipients now have a significant chance for both long-term survival and a reasonable quality of life. These successes have led nearly 80,000 individuals to opt for transplantation as a form of therapy. Unfortunately, the number of organs available has lagged far behind the demand. Every year thousands die while waiting for the gift of life that an organ transplant could provide.

In the case of cadaveric giving, the family of the brain-dead person is asked to donate. There is a serious shortfall in cadaveric organ donations, with only 40–60% of U.S. families consenting to organ recovery. Countries that have adopted the doctrine of "presumed consent" (such as Spain, Austria, and Belgium) have a much higher rate of organ recovery. In these countries, families can "opt out" of donation; if they do not, the organs of deceased family members can be used for transplantation. In most of the rest of the world, families have to "opt in" before organs can be used for transplantation. "Presumed consent" countries that require "opting out" obtain more than 40 donations per million population, as contrasted with half that amount elsewhere. The lower rate is obviously not adequate for meeting current needs.

The number and rate of donations have reached a plateau and leveled off following the enforcement of lower speed limits for automobiles and the introduction of seat belt laws. It is said that donation is a middle class, suburban phenomenon; those groups donate at a somewhat higher rate than others. Why is the rate of donation lower among the poor and in the big cities? We truly do not know. Education, family cohesiveness, trust in medicine, and moral and religious sensibility may all play important roles.

In light of the gap between organ need and organ donation, we are beginning to consider various forms of financial incentives to families as a stimulant for donation (1, 2). I am not re-

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ferring to the token $399 that the state of Pennsylvania has offered for funeral expenses. That amount would hardly pay for a plain pine coffin. Nor am I referring to the more than $10,000 state income tax credit that the Wisconsin senate approved in January 2004 (3). That incentive would be of little use to the poor. I am referring to a substantial amount, to be included in the financial transactions that occur during the transplant process.

Organ transplantation involves payments of large sums of money. Huge sums go to the hospitals, the transplant surgeons, the physicians, the ancillary staffs and the insurance companies. And most of the money actually goes to the pharmaceutical industry. Many millions of dollars flow into their coffers for the immunosuppressants, antihypertensives, antibiotics, anticholesterols, antacids, and so on, that recipients routinely receive in the course of their treatments. The only people who are not being remunerated are the families of the donors. They alone are being asked to be altruistic.

Just try to do a transplant today on an uninsured patient. I can assure you, the patient will not get through the front door. Medicaid will pay for dialysis treatment of an uninsured alien. But Medicaid will not pay for his or her transplant.

What would be the harm of providing a payment to the donating family of, let's say, $20,000? A liver transplant can cost upward of $300,000, a heart transplant $200,000, and a kidney transplant more than $100,000. In kidney transplantation, even the insurance company would benefit from the payment, since they would no longer have to pay for dialysis therapy.

The most controversial remuneration of all is payment to a living donor who has no relationship to the recipient. Because of the organ shortage, most centers in this country accept the donations of living donors who are related, or emotionally related (for example, a spouse or a friend) as the source of transplant organs. In situations where there is an obvious relationship between the donor and recipient, people find no violation of ethical principles. In spite of the inherent risks of donating a kidney or a segment of liver, and the pressures and emotions related to the desire to save a loved one, these organ donations are found acceptable.

But, what of the donor who has no obvious relationship to the recipient? What should we say of someone who only wants to donate an organ to someone with the means to pay for it, perhaps out of financial desperation? About twenty years ago, a foreign-born nephrologist at our institution offered me the opportunity to perform more than two hundred kidney transplants each year. He proposed bringing donor-recipient pairs from his country to our hospital for the surgery. I was to be paid a sizable sum. The apparently wealthy recipients would pay all the involved expenses, and each donor would receive approximately $2,000 for his or her kidney. Apparently, $2,000 was then a substantial sum for a poor person in his country. According to my nephrologist friend, that amount of money would change the donor's life and the standing of his family for generations. Yet even aside from the legal considerations, I rejected the offer outright, because it included no assurance of the donor receiving adequate long-term aftercare. I also felt a sense of revulsion at the idea of a poor, desperate individual peasant being used in this manner by some wealthy businessman or aristocrat.

Nowadays, this form of commercialism is prevalent in the Third World, where either there are no laws prohibiting these transactions or existing laws are not enforced. I shall not address those practices. Instead I want to consider payment for organ donation in an ideal situation. I want to consider the situation where the donor and recipient are carefully selected and carefully matched, and where the operation is well controlled. The donor would be offered long-term care, and the recipient would pay the donor a significant sum. There would be no "middle-men" or brokers involved, and the allocation process would be carefully controlled by the national or regional organ allocation mechanism. Under such circumstances, would it be ethically acceptable for one individual to use another for his own survival and well-being? Would the infliction of pain and suffering on one individual be justified by the benefit to another individual? Should someone with the financial wherewithal be allowed to purchase transplant priority? Does allowing such financial transactions undermine what has been a truly altruistic practice? Would payment to living donors inevitably undermine the public's faith in the process?

Let us examine the proposal in light of the ethical principles involved, to see if they would be violated. But first, I would like to rule out several factors that would be inconsistent with the organ exchange ideal that I imagine:

1. **The donor comes from a country where aftercare is deficient or unavailable.** Such a situation would subject the donor to an

unacceptable risk of harm and would therefore exceed a reasonable balance of harms and benefits.

2. **Third-party brokers, profiteers, or entrepreneurs are involved in the transaction.** Removing any portion of the transplant process from the oversight of medical professionals would remove it from the fiduciary relationship that assures that the donor's life and health would be safeguarded. And commercialism introduces possibilities of exploitation and conflict of interest.

3. **The donor does not truly understand the nature of the donation and the potential risks involved.** Evaluation of the donor by an impartial psychiatrist would be a crucial element in assuring that the donor is making an informed choice that reflects personal values and priorities.

4. **There are bidding wars for organs.** The assurance of donor and recipient safety must be a crucial feature of living donor transplantation. Organ auctions could compromise long-term safety or lead to unexpected and untoward outcomes of living donor transplantation. Auctions can only assure price compatibility between buyer and seller. While the selling price should be set high enough to elicit donors, the larger process must take into account the costs of long-term care and emergencies such as primary non-function of the transplanted organ, or organ rejection. Because the transplantation community has the ultimate responsibility for the careful management of these situations, the transplant community must have oversight of any financial exchange.

I would like to summarize the considerations that incline me to accept payment to organ donors in the ideal situation.

1. **Autonomy.** Certainly the donor and the recipient have the right to proceed if those involved in their care are assured that they have freely accepted the transaction with a complete understanding of the risks and benefits involved.

2. **Beneficence.** Both the donor and the recipient stand to gain from their contract, as does everyone else on the waiting list below the recipient. All of the others waiting for a cadaveric organ will benefit by moving up a notch in the process.

3. **The "do no harm" principle (*primum nolle nocere*).** There is obviously some harm done to the donor in the surgery involved in organ donation. There is also the immediate exposure to surgical risks, and the certain disfigurement and loss of an organ. Also there are possible long-term consequences of organ loss. These risks of harm are so well defined in the kidney transplant experience that donors can be assured that the risks, both long- and short-term, are minimal. The risks associated with the liver, lung and pancreas donation process are not as well defined. Perhaps this element of uncertainty justifies a moratorium on these donations until the risks can be carefully assessed in well-controlled clinical studies.

4. **Justice.** I am less confident about whether an ideal organ payment system will conform to the basic principle of fair and equitable distribution of benefits and burdens. The main benefit of payments for organ procurement would go to relatively privileged individuals. They would get transplant organs more readily than others, in addition to all the other privileges that accrue to the wealthy (e.g., better homes, health care, service, etc.). Yet no one else would be harmed by the paid organ donation, unless there is a general loss of faith in the donation process, with a fall in the rate of altruistic giving. This is an empirical question that can only be answered by a trial.

It is clear that I have changed my position somewhat, on this form of donation. I have accepted the libertarian thesis that selling one's organs does not necessarily violate the right of self-determination, and should fall within the protected privacy of free individuals on the basis of the principle of autonomy. I have also been persuaded by pragmatic and utilitarian considerations—the current system is failing, and the benefits for all recipients of an increase in available organs outweigh most objections.

Of course, I would insist on controls. The donor must be healthy, both physically and mentally, as determined by competent physicians and psychiatrists who are not directly involved in the transplant process. We must be assured that the donor fully understands the risks involved and must sign a statement demonstrating true informed consent. Paid donors must be guaranteed long-term medical care and life insurance for themselves and their families in the event that complications occur. The transplant should be controlled by medical professionals and medical agencies that are intimately involved in transplantation and that can administer the process with due care and impartiality.

I offer a final personal note. I am not entirely pleased that I have had to reach this decision. I would certainly prefer that an ample source of cadaveric organs be available to those in need. Available organs would allow us to avoid the dilemmas of living organ donors and paid donations. But for the time being, while my patients are dying for want of an organ, I have accepted this libertarian, utilitarian approach. We do not live in ivory towers. In life, we have to make hard decisions and accept the consequences when all of our options have serious flaws.

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Payment for Egg Donation and Surrogacy

Bonnie Steinbock, Ph.D.

Abstract

This article examines the ethics of egg donation. It begins by looking at objections to noncommercial gamete donation, and then takes up criticism of commercial egg donation.

After discussing arguments based on concern for offspring, inequality, commodification, exploitation of donors, and threats to the family, I conclude that some payment to donors is ethically acceptable. Donors should not be paid for their eggs, but rather they should be compensated for the burdens of egg retrieval. Making the distinction between compensation for burdens and payment for a product has the advantages of limiting payment, not distinguishing between donors on the basis of their traits, and ensuring that donors are paid regardless of the number or quality of eggs retrieved.

Key Words: Egg donation, ethics, commodification, payment, coercion, exploitation, informed consent, altruism, families.

BOTH PAYMENT FOR EGG DONATION and payment for surrogacy raise ethical issues. I will address only egg donation, for two reasons. First, more has been written about surrogacy than about egg donation. Second, and more important, the two practices raise very different ethical issues. Surrogacy, or contract pregnancy as some prefer to call it, involves giving birth to a child and then waiving one's rights to custody of that child. In a few well-publicized cases, surrogates have changed their minds and attempted to keep the children. This has never, to my knowledge, occurred with egg donation. This is because there is a huge psychological and emotional difference between giving someone else your egg to gestate and deliver a baby, and gestating and delivering a baby yourself and then giving that baby to someone else. Indeed, in most cases, the egg donor does not even know if a child resulted from her donation. While a donor certainly should think about how she will feel about the possibility that there will be a child, or children, genetically linked to her out there in the world, she does not have to contemplate surrendering a child to whom she has given birth. Additionally, a child born from a surrogate arrangement may feel abandoned by the biological mother, just as an adopted child often does. The feelings of rejection by such children are likely to be compounded by the recognition that the birth mothers conceived them and relinquished them for money. It is implausible that a child conceived through egg donation would feel the same way. Finally, whatever may be wrong with commercial egg donation, it cannot plausibly be characterized as "baby selling."

A Terminological Point: "Donors" vs. "Vendors"

Some view the term "commercial egg donation" as an oxymoron. Thomas Murray (1) writes, "Despite the repeated reference to 'donors' of both ovum and sperm, paying individuals for their biological products makes them vendors, not donors." He recommends that the term "AID" (artificial insemination by donor) should really be "AIV" (artificial insemination by vendor). In response, some maintain that paying gamete providers does not make them vendors, because they are not being paid

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for a product, but are being compensated for their time, inconvenience, and risk. I will have more to say about this later. In the meantime, I continue to use the term "donation" even when referring to the commercial enterprise, not because I want to prejudge the question of whether payment is for the product or compensation, still less to prejudge the question of moral acceptability, but simply because it is accepted usage.

Law and Morality

One important distinction is between the legality and the morality of egg donation. While legality and morality are not entirely separate, and arguments for making something illegal are often moral arguments, the two often raise different issues. In Germany, Norway, Sweden, and Japan, the use of donor eggs is illegal (2). It is unlikely that egg donation could be banned in the United States, because such a ban would probably violate the constitutional right to privacy (3). What about banning payments to egg donors? In Canada, there is proposed legislation to ban the "buying and selling of eggs, sperm and embryos, including their exchange for goods, services or other benefits...." The Minister of Health adds (4), "This prohibition will come into force over a period of time to ease the transition from the current commercial system to an altruistic system." Legislation in the United States banning payment to egg donors might not withstand constitutional scrutiny. It would depend on whether or not banning payment is viewed as an undue restriction on procreative liberty. The point I am making is that even if there are serious moral objections to commercial egg donation, there could be constitutional barriers to making it illegal.

When the topic is the morality of a controversial practice, an important question is whether it is morally permissible. However, this is not the only question we can ask. Margaret Little characterizes moral permissibility as "the thinnest moral assessment." Writing about abortion, Little (5) says, "... many of our deepest struggles with the morality of abortion concern much more textured questions about its placement on the scales of *decency*, *respectfulness*, and *responsibility*. It is one thing to decide that an abortion was permissible, quite another to decide that it was *honorable*; one thing to decide that an abortion was impermissible, quite another to decide that it was *monstrous*." So even if paying egg donors is morally permissible, it does not follow that it is desirable, praiseworthy, or decent.

The practice of commercial egg donation has come under severe criticism, but before examining the ethics of paying donors, we need to see if there is something intrinsically wrong about donating one's gametes to others for the purposes of reproduction, even in the absence of any payment.

Noncommercial Gamete Donation

The Roman Catholic Church opposes gamete (ovum or sperm) donation because of its views on the unity of sexual intercourse and procreation. Sexual intercourse without openness to procreation is wrong, the Church claims (hence its opposition to birth control), but equally so is procreation without sexual intercourse (hence its opposition to most forms of assisted reproduction). Even the "simple case" of *in vitro* fertilization (IVF), where the husband and wife provide the gametes and the resulting embryos are implanted in the wife's uterus, is impermissible, according to Catholic teaching. The wrong is compounded in gamete donation, as the introduction of "a third party" violates the unity of marriage. In addition, according to the Rev. Albert Moraczewski, egg donation is demeaning to women. "A donor woman is not really being treated as a person," he said. "Whether she is paid or acts out of kindness, her egg is being used, so she is not fully treated as a person whose reproductive capacity should be expressed as a result of the love of her husband" (6).

But why is egg donation demeaning? Presumably blood donation is not demeaning, and does not fail to treat the donor as a person. What is the difference? The answer, according to the Vatican, is that egg donation involves a wrongful use of reproductive capacity. But then to characterize egg donation as demeaning is not to give a reason why it is wrong; rather, egg donation is demeaning because it is wrong. To see egg donation as demeaning, one must accept the principle that reproductive capacity should be exercised only through a sexual act in the context of a loving marriage. And that principle is justified by the supposedly indissolvable unity of sex, love and procreation. There is nothing inconsistent or incoherent in this view, but it is unlikely to be persuasive to non-Catholics who accept contraception or assisted reproduction.

A different objection to gamete, specifically sperm, donation comes from Daniel Callahan.

AID is "fundamentally wrong," according to Callahan, because a sperm donor is a father, who has all the duties of any other biological father, including rearing responsibilities. Sperm donation, according to Callahan, is as irresponsible as abandoning a woman when she becomes pregnant. He writes (7):

> The only difference between the male who impregnates a woman in the course of sexual liaison and then disappears, and the man who is asked to disappear voluntarily after providing sperm, is that the latter kind of irresponsibility is, so to speak, licensed and legitimated. Indeed, it is treated as a kindly, beneficent action. The effect on the child is of course absolutely identical—an unknown, absent father.

Certainly, it is true that the child born from sperm donation does not know his or her genetic father. But it is not true that these children are fatherless, as is true of most children whose fathers abandon their mothers. They do have fathers—the men who are raising them. Why, one may ask, is it irresponsible to enable an infertile man, who wants very much to parent a child, to become a father? Sperm donors, it may be said, do not evade or abandon their obligations, as do men who abandon women they have impregnated, but rather transfer their rearing rights and duties to others. These others may be men or they may be single women or lesbian couples, who are increasingly using sperm donation. Is it wrong to donate sperm if the resulting child will grow up in a fatherless home? Is this an abandonment of one's responsibility as a father? In my view, this depends on whether the child can be expected to have a reasonably good life. There is evidence that children in single-parent households are at a disadvantage (since it is usually more stressful to raise a child on one's own), but growing up in a lesbian family does not appear to have a negative impact on quality of parenting or children's psychological development (8). Many lesbian mothers attempt to mitigate the disadvantages of not having a father by making sure that there are other men in their child's life.

David Benatar (9) acknowledges that "gamete donation is not a unilateral abandonment of responsibility," but rather a transference of responsibility. Nevertheless, Benatar thinks that the responsibility of child rearing is one that should not be transferred, that doing so shows a lack of moral seriousness. Certainly, transferring child-rearing responsibilities without much thought is reprehensible; one thinks of Rousseau, who took five illegitimate children he had with his mistress to an orphanage. But is that what gamete donors do? Sperm and ova are not, after all, children. In my opinion, gamete donors do not give others their children to raise. Rather, they enable people who very much want to have children of their own to do so by providing them with genetic material. A woman who does not have eggs can still experience gestation, birth, and lactation, giving her a biological, if not genetic, connection to her child. In addition, if her husband's sperm is used, he will also have a biological connection to the child.

The Need for Egg Donation

Egg donation began in the early 1980s; the first pregnancy using this technique was reported in Australia in 1983 (2). Ovum donation is offered to women with three types of reproductive problems. Women in the first group lack functioning ovaries. Those in the second group have no detectable ovarian failure, but they do not achieve pregnancy through IVF. These include women for whom ovarian retrieval is unsuccessful and those who cannot undergo egg retrieval, usually because scarring or endometriosis prevents access to the ovaries. A third group of women use donated eggs for genetic reasons.

When egg donation was first introduced, the eggs came from either close friends or relatives, in a practice known as "known donation," or they came from women who were undergoing IVF themselves. Because the number of eggs retrieved exceeded the number of embryos that could be safely implanted, women undergoing IVF often had extra eggs, which they were often willing to make available for donation. This source greatly diminished when it became possible to freeze embryos (egg freezing is still experimental). Another source of eggs was from patients undergoing tubal ligation (6). However, the demand for donors soon outstripped these sources and programs began to recruit women from the public at large through advertising. Thus, commercial egg donation came into being.

The main reason for the increasing demand for egg donors is that, for some women, using an egg donor significantly improves their chances of becoming pregnant. "An infertile woman using her own eggs for *in vitro* fertilization has about a 15 to 20 percent chance of becoming pregnant, less if her ovaries are scarred by infection or endometriosis or are simply too old to function effectively. With an egg donor, her chances of bearing a child shoot up to 30 or even 40 percent" (10). The older the woman, the greater are her chances of becoming pregnant if she uses donor eggs. According to one article (11), "a 44-year-old woman attempting IVF with her own eggs at Pacific Fertility has a 3.5 percent chance of becoming pregnant. If that same woman uses a donor egg from a younger woman, her chances of giving birth are 50 percent." For some women, therefore, egg donation provides the only realistic option for having a child.

What Is Involved in Egg Donation?

The process is very time-consuming. First, the prospective donor must be accepted into a program; this may involve several visits. She will undergo physical and gynecological examinations, blood and urine tests, and a psychological examination, and participate in discussions of the responsibilities involved in becoming a donor. Because eggs cannot be frozen (or "banked"), the actual donation cycle will not occur unless the prospective donor is accepted, is matched with a recipient, and has given her consent.

The following is typical of the medical process undergone by donors. First, the donor may take a prescribed medication for one or more weeks to temporarily stop her ovaries' normal functioning. This makes it easier to control her response to fertility drugs which will be used later in the cycle. She will be given an injection by the physician or instructed in how to inject the medication daily at home. The medications may cause hot flashes, vaginal dryness, fatigue, sleep problems, body aches, mood swings, breast tenderness, headache and visual disturbances.

Next, medications must be injected over a period of about 10 days to stimulate her ovaries to mature a number of eggs (typically 25 – 30) for retrieval. Frequent early morning transvaginal ultrasound examinations and blood tests (about every 2 – 3 days) are needed to monitor the donor's response to the drugs, and adjust the dose as needed. While using injectable fertility drugs, the donor may experience mood swings, breast tenderness, enlarged ovaries and bloating. Occasionally, these medications result in ovarian hyperstimulation syndrome, in which the ovaries swell and fluid builds up in the abdominal cavity. If the hyperstimulation is mild, it will recede after the donor's next menstrual period. If the hyperstimulation is moderate, careful monitoring, bed rest, and pain medication may be necessary. Severe hyperstimulation is infrequent, but may cause serious medical complications, such as blood clots, kidney failure, fluid accumulation in the lungs, and shock. This condition can be life-threatening. Severe hyperstimulation occurs in about 1 – 10% of IVF cycles. It may result in one or both of the donor's ovaries having to be removed.

The mature eggs are removed from the ovaries in a minor surgical procedure called "transvaginal ovarian aspiration." It is usually done in the physician's office. First, the donor will be given painkillers or put under intravenous sedation. Then, the physician inserts a needle through the vagina to aspirate the eggs out of the follicles. According to one description, "The procedure takes 15 to 60 minutes and, except for grogginess and some mild pelvic discomfort, there should be no aftereffects (12)." Some may experience more than mild pelvic discomfort: one egg donor described it (on a website for donors) as "feeling like somebody punched you in the stomach." Many donors find the actual retrieval less unpleasant than the side effects from the drugs.

Why Do Women Want to Donate?

Given the rigors of egg donation, why would a woman who was not undergoing IVF or tubal ligation be willing to undergo egg donation for strangers? Some donors are curious about their own bodies and fertility. They want to know if their eggs are "good" (10). Some have a personal reason for helping, such as having friends or relatives who have struggled with infertility or have undergone miscarriages. Others are attracted by the idea of giving "the gift of life," as the advertisements for egg donors put it. One donor explained it as follows, on a donor website: "I can't even describe how it felt to know that in some small way I helped this couple achieve a huge dream in their life." But while most egg donors are motivated in part by altruistic considerations, most women would not be egg donors for strangers without financial compensation. Many say that egg donation would be impossible if they were not compensated for lost work time, transportation, daycare costs, and the like. However, most donors think that reimbursement for pecuniary expenses alone is not enough. They think that it is only fair that they should receive reasonable compensation for what they go through in order to provide eggs: the inconvenience, burden, and medical risk they have endured.

How Much Payment?

Compensation has been increasing rapidly over the years. In the mid-1980s, egg donors were paid only about $250 per cycle. Today, the payment is usually between $1,500 and $3,000—depending on the location of the clinic. In an effort to attract donors, some clinics offer substantially more. In 1998, Brooklyn IVF raised its donor compensation from $2,500 to $5,000 per cycle to keep pace with St. Barnabas Medical Center in nearby Livingston, New Jersey. "It's obvious why we had to do it," says Susan Lobel, Brooklyn IVF's assistant director. "Most New York area IVF programs have followed suit" (13).

Donors with particular attributes, such as enrollment in an Ivy League college, high SAT scores, physical attractiveness, or athletic or musical ability have allegedly been offered far larger sums. "The International Fertility Center in Indianapolis, Indiana, for instance, places ads in the *Daily Princetonian* offering Princeton women as much as $35,000 per cycle. The National Fertility Registry, which, like many egg brokerages, features an online catalogue for couples to browse in, advertises $35,000 to $50,000 for Ivy League eggs" (13). In March 2000, an ad appeared in *The Daily Californian* (the campus newspaper for the University of California, Berkeley), which read, "Special Egg Donor Needed," and listed the following criteria for a "preferred donor": "height approximately 5'6", Caucasian, S.A.T. score around 1250 or high A.C.T., college student or graduate under 30, no genetic medical issues." The compensation was listed as $80,000 "paid to you and/or the charity of your choice." In addition, all related expenses would be paid. Extra compensation was available for someone especially gifted in athletics, science/mathematics or music.

Perhaps the most well-known instance of commercial egg donation is Ron Harris's web site, www.ronsangels.com, which offered models as egg donors, "auctioning their ova via the Internet to would-be parents willing to pay up to $150,000 in hopes of having a beautiful child" (14). A subsequent story suggested that the "egg auction" might just be a publicity stunt to attract people to an erotic web site, a claim that a spokesman for Mr. Harris denied (15). Some infertility experts maintain that the ads offering large sums of money for special donors are not genuine offers, but rather a "bait and switch" tactic to recruit donors. Donors who respond are told that the ad has been filled, but that there are other recipients (offering substantially less money) seeking donors. *The Daily Californian* ad mentioned above specifically stated, "This ad is being placed for a particular client and is not soliciting eggs for a donor bank." I recently e-mailed the International Infertility Center in Indianapolis, asking them if the fee of $35,000 mentioned in the news report was actually paid to anyone. They responded that the "high-profile client" on whose behalf they had advertised did not find an ovum donor meeting the requirements, and so no ovum donor was compensated $35,000 for a cycle. I have not been able to discover if any "special donors" have received the sums in the ads.

Most people would distinguish between reasonable compensation and offering $30,000 or more to special donors. What explains the negative reaction most people experience when learning of these huge offers? Perhaps we think that people who are so intent on getting superior eggs (or "designer genes") will be incompetent parents. Instead of anticipating having a child to love, it seems that the couple is focusing on the traits their child will have. They are not satisfied with having a healthy child, which is the reason for genetic screening of donors. Nor is their aim simply to have children who resemble them, something that adoptive parents also usually want. These are reasonable requests, whereas seeking donors from Ivy League schools, with high SATs and athletic ability, indicates something else. The placers of these ads want, and are willing to pay huge sums to get, a "superior" child, and this seems inconsistent with an ideal of unconditional parental love and acceptance.

Moreover, anyone who thinks that it is possible to guarantee that a child will be brilliant, athletic, musically talented, or even blond haired and blue eyed, is likely to be disappointed. According to several prominent geneticists writing in *The New Republic* "despite what your high school biology teacher told you, Mendelian rules do not apply even to eye color or hair color" (16). Even genetic diseases widely considered to follow Mendelian rules, like sickle-cell anemia, may be more or less severe, due to the interaction with other genes in the genome. Predicting or determining non-disease-related traits like intelligence, athletic ability, or musical talent is even less likely, as there are probably thousands of genes that play a role. Finally, the interaction of genes and the environment makes it very difficult to know in advance what phenotypic traits an individual will have. This is not to deny that traits like intelligence or athletic ability have a genetic component, but only to say that they cannot be guaranteed by the choice of an egg donor (who, after all, only provides half the genes). We may well worry about the welfare of a child who fails to live up to parental expectations, after the parents have spent all that money.

The welfare of offspring is a legitimate concern, despite philosophical worries over how to conceptualize it (17). If commercial egg donation led to poor parenting or had adverse effects on the parent-child relationship, that would be an important moral objection. Yet such an objection might not justify the conclusion that the buying and selling of eggs is morally impermissible, still less that it should be legally banned. For we do not think that procreation is morally permissible only for ideal parents. Nevertheless, concern about effects on parenting and the parent-child relationship fall under the heading of "thick" moral assessments, and may be legitimate.

On the other hand, it is possible that couples who place the ads understand that they cannot determine their children's traits and that they do not have false expectations. Nevertheless, they might say, they want to give their child an advantage, a better chance at traits likely to help the child in life. It is not that they can only love a tall, brilliant, athletic child, they might say, but rather than they are well aware how advantageous such traits can be. Why, they might ask, if they have the money to spend, should they not use it to give their child the best chance in life? Indeed, some have argued that prospective parents are morally required to have the best child they can (18).

The Human Fertilization and Embryology Authority (HFEA) in the U.K. cited "the physical and psychological well-being of children born from egg donation" as a reason to ban all payments, not just large ones, to egg donors. According to one member of HFEA (19), "Children produced by egg donation could be adversely affected psychologically if they knew that payment had been made as part of their creation." This seems not only speculative, but implausible. Children may be psychologically harmed if they sense that their parents' love is contingent on their having certain traits, but why would a child be psychologically harmed by learning that the woman who provided the egg from which he or she was conceived received payment? It seems to me that this concern stems from an inappropriate analogy with commercial surrogacy. Children might well be upset to learn that their biological mothers gave them away for money, but it seems implausible that any child would have similar feelings about an egg donor. This being the case, it is hard to see why children would be affected by whether donors were paid or not.

Another moral objection to these ads is that they are elitist and violate a principle of equality. There is something offensive in the idea that the eggs of Princeton women are worth $50,000, while the eggs of women at Brooklyn College are worth only $5,000. (John Arras has jokingly suggested that perhaps *US News & World Report* should include how much their coeds can get for their eggs in their rankings of colleges [personal communication].) Yet it is not clear why we should be offended at the difference in the price put on eggs if we are not offended by differences in employment opportunities or salary.

Some people are disturbed not only by the payment of large sums to egg donors, but by any payment at all. Commercial egg donation is criticized on the grounds that this "commodifies" the human body or "commodifies" reproduction.

Commodification

To commodify something is to give it a market price. That in itself is not a bad thing. We could not buy our groceries or clothes or the morning paper if they did not have a market price. If some things should not be commodified, we need a rationale for this. This is not always forthcoming. As the guest editors of a recent special issue on commodification in the *Kennedy Institute of Ethics Journal* say (20), "Unfortunately, a great deal of the talk about 'commodification' has been clumsy and sloppy. The term has been used as a magic bullet, as if saying, 'But that's commodification!' is the same as having made an argument."

The challenge is to distinguish legitimate activities in which the human body or its abilities are used, from those thought to be illegitimate. As Ruth Macklin has put it (21), "Every service in our economy is sold: academics sell their minds; athletes sell their bodies.... If a pretty actress can sell her appearance and skill for television, why should a fecund woman be denied the ability to sell her eggs? Why is one more demeaning than the other?"

Those who tend to oppose commodification typically portray those who are skeptical about its moral wrongness as being enamored of the market, of thinking that freedom of choice is the only or the most important moral value. They say, "...there are some categories of human activities that should not be for sale (22)." But this, even if true, is unhelpful. We want to know *what* things and activities should not be for sale and *why*? Michael Walzer gives voting as an example of a market exchange that should be blocked. Citizens may not sell their votes or vote a certain way for a price (23). This is so even if the exchange is fully voluntary and even if it makes both parties better off. The reason why votes may not be sold is that this conflicts with the rationale for having the institution of voting in the first place. Voting is intended to express the will of the people in a democracy. Democracy is subverted if votes can be bought.

What we want, then, is a similarly persuasive rationale for the wrongness of selling human body parts. Suzanne Holland attempts to give one. She writes (24):

> For many of us, our sense of the dignity of humanity is fundamentally disturbed by the suggestion that that which bears the marks of personhood can somehow be equated with property. We do not wish to have certain aspects of that which we associate with our personhood sold off on the market for whatever the market will bear.

Eggs should not be seen as property, according to Holland, because the human body is "inalienable." But what does this mean? To call rights "inalienable" is to say that they cannot be taken away from us, though Joel Feinberg has argued that we can waive them (25). If calling the human body "inalienable" means that others cannot use my body or body parts without my permission, that is undeniable. But why does this imply that I may not sell my gametes? If "inalienable" just means "may not be treated like property," then Holland has not given a reason why eggs are not property, but rather a tautology.

The fact that something is a human body part does not make it obviously wrong to sell it. In the novel *Little Women*, Jo sells her hair to raise money for her father, who is serving as a chaplain in the Union Army. Surely that was not morally wrong of Jo, nor demeaning to her. Indeed, her willingness to part with "her one beauty" is an unselfish and noble gesture. If selling one's hair is morally permissible, but selling one's gametes is not, what is the moral difference?

It might be thought that I am missing an obvious point. Selling one's hair is not wrong because hair is unrelated to sex and reproduction. Selling one's eggs is akin to selling one's body in prostitution, and "we all know" that prostitution is wrong. Actually, prostitutes do not literally sell their bodies, since they do not relinquish control. It is more accurate to say that they rent them out, or rather that they perform sexual acts in exchange for money. Most of us believe that this is wrong, but this belief may be due in part to sexual puritanism. Perhaps the distaste we feel for prostitution stems (at least in part) from the way prostitutes have typically been regarded in patriarchal societies—as women of no value, undeserving of respect. Imagine a world in which those who provided sexual services were treated with as much respect as psychotherapists, trainers, and masseurs are in our society. It might be that, under such conditions, prostitution would not be as degrading. But even if this argument is invalid, there is a vast personal difference between these two types of "selling," and there is no obvious reason why paying egg donors is incompatible with treating them with respect.

There are two more reasons why selling eggs might be wrong. Providing eggs is both painful and risky. Perhaps offering money to women will lead them to take undue risks, opening up the potential for coercion or exploitation. In addition, some argue that payment for eggs inserts the values of the market into the family. I will consider these objections in turn.

The Potential for Coercion or Exploitation

In its report on *Assisted Reproductive Technologies*, the New York State Task Force made the following recommendation (2):

> Gametes and embryos should not be bought and sold, but gamete and embryo donors should be offered compensation for the time and inconvenience associated with donation. Payments to egg donors should not be so high as to become coercive or so low that they provide inadequate reimbursement for time and inconvenience.

Can offering large sums of money for eggs be seen as coercive? That depends on the theory of coercion that one adopts (26). In one theory, to coerce is to make a threat: do this or I will make you worse off. The classic example is the highwayman who says, "Your money or your life." Clearly, potential egg donors are not coerced in this sense, no matter how much money is offered to them. They can turn down the offer and be no worse off than they were.

Perhaps this is too narrow a view of coercion. Perhaps there can be "coercive offers" as well as threats. Consider the following example:

The Lecherous Millionaire: Betty's child will die without expensive surgery, which is not covered by her insurance. Alan, a millionaire, offers to pay for the surgery if Betty will have sex with him.

Alan is not threatening Betty. He will not harm her if she refuses. Yet there is a very real sense in which she has "no choice," and for this reason we might see the offer as coercive. But even if this is true, and there can be "coercive offers," does this apply to egg donation? It might, if the money were offered to terribly poor women whose lives, or the lives of their children, depended on their donating eggs. A woman whose only choice was to give away her eggs or see her child die of starvation might well be seen as the victim of coercion. However, poor women are not usually sought out as egg donors. Typical egg donors are middle-class, often professional, young women. It is simply not true to say that they have no choice but to sell their eggs.

Very large offers of money could be quite tempting to any woman, not just those in desperate need of money. But, as Wertheimer points out, offers are not coercive just because they are tempting. And they are not coercive because they are so good that it would be irrational to refuse. It is not coercive to offer someone a great job at double the salary she is currently earning (27).

However, if offers of large sums of money are not coercive, they may still be criticized as being "undue inducements." Offering "too much" money may be an attempt to manipulate women into becoming donors. The lure of financial gain may lead them to discount the risks to themselves and to make decisions they will later regret. To take advantage of this is a form of exploitation.

It might be argued that we should not attempt to protect adults from irrational assessments or choices they will later regret, because this is paternalistic. However, paternalism involves preventing people from doing what they want on the grounds that this is in their best interest. It is not paternalistic to refrain from taking advantage of someone's susceptibility to temptation.

Some people have tried to meet the charge of commodification by distinguishing between compensating egg donors for their time, risk, and inconvenience, and payment for their eggs. This distinction has been challenged by several commentators, including Ruth Macklin, who writes (21), "If there is something suspect about commodifying human reproductive products, it is similarly suspect to commodify human reproductive services." However, I think there are two reasons to distinguish between payment for time, risk, and inconvenience, and payment for eggs. First, if payment is viewed as compensation for the burdens of egg retrieval, then large payments based on the donor's college, height, or SAT scores would be unjustified. It is as burdensome for a SUNY-Albany student as it is for a Princeton student to go through the egg retrieval process. Additionally, if payment is compensation for the donor's time, risk, and burden, then donors would be compensated regardless of the number or quality of eggs retrieved, whereas this makes no sense if payment is for the product (eggs). Despite Macklin's rejection of the product/service distinction, she makes precisely this recommendation.

If excessive payments exploit donors, so do payments that are too low. Justice would seem to require that the women who go through the rigors of egg retrieval be fairly compensated. Why are only egg donors expected to act altruistically, when everyone else involved in egg donation receives payment? In light of the sacrifices of time, risk, and burden that egg donors make, it seems only fair that they receive enough money to make the sacrifice worthwhile.

Other Worries About Exploitation

Concerns about the exploitation of egg donors are not limited to payment issues. When the New York State Task Force on Life and the Law completed its report on assisted reproductive technologies (2), one of its findings was that there were serious omissions in the process of gaining informed consent of egg donors. Donors did not always know how strenuous donation would be, or how much time it would take. They often had only the vaguest idea about who would pay their expenses, should there be medical complications stemming from donation. In one study, researchers were told by a number of women that all of their follow-up care was provided free of charge, but two women were billed for medical expenses for follow-up care and medical complications even though both were promised that the clinic would cover these costs:

> One woman was promised follow-up care prior to donating, but after the donation, that care was denied. She sought out her own personal physician for a sonogram and had to pay hundreds of dollars out of pocket because she was uninsured at the time. (28)

Another woman fainted at work while taking hormonal injections. She had muscle spasms and started to convulse, and had to stay overnight in the hospital. "The clinic denied that her condition was related to the donation and refused to pay for her hospitalization. She is currently fighting with her own health insurance and worker's compensation over the $3500 bill" (28).

One of the most significant sources of conflict in egg donation is the pressure on health care providers to hyperstimulate the donor to produce the maximum number of oocytes. The more eggs, the better the recipient's chances at implantation, but the greater the danger to the donor of suffering from hyperstimulation syndrome (28). One donor who testified before the advisory committee to the New York State Task Force on Life and the Law revealed that one of her cycles had been stopped, but she had no idea that this was due to excessive stimulation, which had posed health risks to her. She thought that the reason so many eggs had been retrieved was that she was "super-fertile." One of the fertility doctors on the committee said that it was not uncommon for clinics to "flatter" donors in this way, to get them to be repeat donors. Such deceptive treatment of donors is, in my view, a greater source of exploitation, and an area of greater moral concern, than offering payment.

Altruistic egg donation would not necessarily be immune from exploitation. In fact, the true risks and burdens of egg donation might be less likely to be revealed in a voluntary system than in a carefully regulated commercial market, if only because the counseling and screening of donors costs money. Yet altruism can be an appropriate factor. When egg donation imposes little or no extra burden, as in the case of women who are undergoing IVF themselves or women having tubal ligations, there is less reason to compensate women for donating. Altruism in such cases is morally appropriate, as is the case with blood donation, which also involves minimal time and risk. The greater the burdens and risks, the less appropriate is the expectation of altruistic donation.

For some critics, it is not concerns about vulnerable donors that lie at the heart of their objections to commercial egg donation, but rather the effects on the families that are created, and ultimately on society at large.

Threats to Families

Tom Murray writes (1):

> New reproductive technologies are a challenge to our notions of family because they expose what has been at the core of the family to the vicissitudes of the market. At the heart of our often vague concerns about the impact of new reproductive technologies, such as those about the purchase of human eggs, is our sense that they threaten somehow what is valuable about families.

While Murray acknowledges that even noncommercial gamete donation raises "morally relevant difficulties" (presumably those raised by Callahan [7] and Benatar [9], as well as the issue of the introduction of "a third party" into the marital relationship), he thinks it likely that these difficulties are outweighed by the good of creating new parent-child relationships. It is payment that Murray finds morally objectionable. He writes (1):

> If you believe that markets, the values markets exemplify, and the relationships that typify market interactions, celebrate human freedom, and that such freedom is the preeminent good, then none of this should bother you. If, however, you regard families as a sphere distinct from the marketplace, a sphere whose place in human flourishing requires that it be kept free of destructive incursions by the values of the market, paying gamete providers should trouble you.

I think we would all agree that families should be protected from destructive incursions by the values of the market—but which incursions are destructive? Presumably it is okay to pay the people who care for our children: day care workers, nannies, and babysitters. These transactions, supposedly, do not commercialize families. Also, presumably, there is nothing wrong with paying those who provide fertility treatment: doctors, nurses, receptionists, lawyers, and genetics counselors. So what is it about paying gamete providers that is threatening to families? Murray does not say. One can agree with his view (1) that "thinking of children as property, and of family life as essentially a series of commercial transactions, is a grievous distortion," but it is unclear what this has to do with paying gamete donors. Eggs are not children, and buying eggs (or even embryos) is not buying children. Still less is it clear why reasonable compensation to egg providers should turn family life into a series of commercial transactions.

Incomplete Commodification: A Reasonable Compromise

Is there room for compromise between those who prefer an altruistic system of egg donation and those who think that egg donors should be paid? Suzanne Holland suggests we take an approach she calls "incomplete commodification" (24):

> With respect to gamete donors, an incompletely commodified approach could recognize that donors are contributing to something that can be seen as a social and personal good (remedying infertility), even as they deserve a degree of compensation that constitutes neither a financial burden ([if they are paid] too little) nor a [temptation to undergo] health risk ([if paid] too much). I see no reason not to follow the suggestion of [the] ASRM [American Society for Reproductive Medicine] and cap egg donor compensation at $5000.... Allowing some compensation, but capping it at $5000, would reduce the competition for eggs and perhaps curb the lure of advertising that is targeted to college students in need of "easy money."

Not everyone agrees that $5,000 is appropriate compensation. Mark V. Sauer, a reproductive endocrinologist at Columbia-Presbyterian Medical Center, was "shocked" by the decision of St. Barnabas to double compensation from the community standard of $2,500 to $5,000 per cycle: "Even if one considers the time spent in traveling to the local office and waiting for an ultrasound exam to be 'work,' donors now will be earning in excess of $300 per hour. I find it hard to believe that anyone thinks this 'reasonable compensation' according to the recommendations of the Ethics Committee of the American Society for Reproductive Medicine" (29). However, Sauer's figure apparently takes into consideration only the number of hours spent traveling to and waiting at the clinic, together with the time required for the procedure. It does not consider compensation for risk or discomfort, or the time that some donors will have to take off from work or classes due to side effects from the drugs they must take. When these factors are considered, reimbursement of $5,000 may not be an "indecent proposal." Perhaps if, like Sauer, doctors are worried that (29) "most importantly, and most unfortunately, these expenses will have to be passed on directly to our patients, who are already spending considerable sums of money to seek this procedure," they might consider reducing their fees.

If compensation were completely banned, few women would agree to be egg donors. Very little egg donation would occur, and this would be unfortunate for those women who cannot have babies any other way. This is part of the justification for paying egg donors; the other part has to do with treating donors fairly. At the same time, legitimate concerns about the psychological welfare of the offspring created, and the potential for exploitation of donors, speaks to the need to limit payments to amounts that are reasonable and fair.

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Spreading It Around:

Money for Researchers and Research Participants

Rebecca D. Pentz, Ph.D.

Abstract

There is a consensus that inducements for participants in research studies are ethically permitted as long as they are not "undue." The subject of inducements for investigators has not been ethically analyzed. This essay outlines the three models for compensation suggested by Dickert and Grady—market model, reimbursement model and wage-payment model—and argues that this analysis can be fruitfully applied to remuneration for investigators. Currently, investigators are compensated according to the market model, resulting in undue inducement. Investigators should be compensated according to the wage-payment model, as skilled workers, at the rate an internist earns per hour. The wage-payment model avoids undue inducement, but compensates investigators, particularly non-academic investigators who are not salaried, for their time and effort. However, additional safeguards must be erected: investigators must demonstrate research competency for the studies they are to manage; they must understand research ethics; all investigators must be routinely audited; and subjects must be informed of all remuneration that investigators receive.

Key Words: Inducement, ethics, clinical research, pharmaceutical research, compensation, conflict of interest, drug testing, phase I trials, healthy volunteers.

Contrasting stories demonstrate the need to discuss distributing funding appropriately in research. The first is from Georgia, my new home state. Dr. Richard Borison, a professor at the Medical College of Georgia, opened a little drug-testing shop with his friend Bruce Diamond, a pharmacologist. They ran trials for top pharmaceutic companies such as Zeneca, Johnson and Johnson, Smith-Kline Beecham, Bristol-Myers Squibb, Lilly and Glaxo Wellcome. Both Borison and Diamond had promising academic careers, Borison having published 85 scholarly articles by the time he finished his residency and Diamond having collaborated on over 50 research projects. Borison was a full professor by 1988, and later was chair of psychiatry. With his drug-testing business booming, Borison opened a separate office in a biotech park, earning over $10 million. Non-medical employees treated patients, read electrocardiograms and signed medical records. Eligibility criteria were stretched; the local institutional review board (IRB) was avoided. All this proceeded unchecked until an employee moved to another research office and quickly found out that that was not the way research was conducted. The former employee's new boss alerted the medical college (1). Drs. Borison and Diamond are not alone, joining the company of the infamous Dr. Fiddes, who stored other people's urine in his refrigerator in order to have urine with the proper acidity available for the auditors (2).

Hoi Yan Wan, a 19-year-old student at the University of Rochester, volunteered for a smoking and air pollution study that involved a bronchoscopy. She was paid $150. She reacted to the high dose of lidocaine used to anesthetize her throat for the procedure and died later that day of cardiac arrest (3). In a similar case, Bernadette Gillcrist, a 23-year-old nursing student who lied about her anorexia nervosa and two previous cardiac arrests in order to earn $1,300 in a sleep study, also died of a cardiac arrest (4).

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Subjects

Much attention has been paid to the ethical framework for compensating participants in research studies. What has not been analyzed is the ethical way to compensate physician-researchers for their contribution to studies. I will argue that the analysis used for participants must now be applied to researchers and that additional safeguards must be erected for both groups.

An ethical consensus has developed that research participants may be paid or otherwise compensated for their participation, as long as the inducement is not "undue." The Belmont Report defines "undue" as "an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" and warns that otherwise acceptable offers may be considered undue influence for some vulnerable populations (5). The National Commission for the Protection of Human Subjects states that "limiting remuneration to payment for time and inconveniences of participation and compensation for any injury resulting from participation "is the best way to keep inducement due" (6). Although the "Common Rule" is not specifically cited, the Food and Drug Administration agrees that "the IRB should review both the amount of payment and the proposed method and timing of disbursement, to assure that neither are coercive or present undue influence" (7).

Dickert and Grady offer an excellent analysis of three models of compensation, the market model, the wage model and the reimbursement model. They indicate a preference for the wage model, partly because it avoids undue inducement (8). In the market model, the market determines how much the subject is paid, with higher payments for top priority trials for which subjects are difficult to recruit, and lower or no payment for those trials with more than enough recruits. Dickert and Grady complain (and I agree) that this model has ethical drawbacks, including different payments for the same work, the possibility of undue inducement for unpopular experiments, competition among researchers for participants, and the potential to coerce vulnerable groups that have few options. Dickert and Grady also reject the reimbursement model, the one most widely used today, which merely reimburses subjects for their expenses. They judge this model to be too restrictive, potentially not attracting enough research participants, and being inequitable if participants are reimbursed for time lost at work. Since participants' day jobs pay differently, they have to be reimbursed at different rates to match what they earn at their jobs. I judge this model to be an acceptable ethical model, if time lost at work is not reimbursed, but I agree with Dickert and Grady that the third model, the wage-payment model, is preferable.

The wage-payment model treats research participants as unskilled labor and argues that they should be paid at, or slightly above, the minimum wage. This model avoids inequitable pay for the same work and undue inducements, recognizes the contribution that research participants make, and reduces or eliminates the financial sacrifice resulting from research participation. Others recommend the wage-payment model as well (4, 9–11).

There are several important objections to the wage-payment model. Some assert that it commercializes research and eliminates altruism. In a small study of 67 research participants recruited for a vaccine trial, some of whom entered the trial and some of whom did not, Russell, Moralejo and Burgess found that most participants (57%) did not think that either patients or healthy volunteers should be paid. One person espressed the view that "people should volunteer because they want to help. Not because they will receive a fee!" (12). On the other hand, people who contribute to society's welfare are typically recognized with pay (e.g., fire fighters, police, and sanitation workers). Further, receiving pay is compatible with altruistic motives. In a wage-payment model, wages would not be paid for all research participation, allowing altruism full play in the unpaid experiments. For trials that pay wages, potential participants who choose research work rather than other unskilled jobs could do so for altruistic reasons. Also, it is naïve to believe that research is not already commercialized for researchers, who can hold patents, biotech stock options, and lucrative consulting positions. A wage-payment model offers some, albeit a small amount, of the available money to the participants.

A second objection is that wage-payment will increase the enrollment of persons in a lower socio-economic group, thus shifting the burden of research unfairly to a vulnerable group in society. This possibility is a concern, though as Robert Levine states, "one notes without serious dismay that corporate executives are not competing for employment as office secretaries, meter readers, jurors or research subjects" (11). Several safeguards should be erected to minimize this potential harm. Some have suggested that only studies with an increment above minimal risk should be considered for wage-payments (9, 11). The burden borne by low income groups would then not include great risk. I agree with this position, in most cases, but will make the case below that certain therapeutic studies that are above minimal risk should be included. Dickert and Grady, who include more risky studies as appropriate for the wage-payment model, suggest that payment should not escalate according to risk (8). Since greater risk would not entail more payment, a potential participant could compare studies and decide which risks are acceptable to him or her. Others argue that, rather than increasing burden, offering wages gives those in lower socio-economic groups more choices and options for improving their situation (13). Offering wages does increase options, but this response does not address the inequity in the share of research burdens. The well-off have more options and therefore are not as attracted to low-paying research. My own position is that, since lower socio-economic groups are currently underrepresented in research, payment of wages may improve the balance. Empirical studies are needed to determine if this hypothesis is correct.

A related concern is that minimum wage will be an undue inducement for certain groups. For Bernadette Gillcrist, who lied about her cardiac history, $100 a day appears to have been an undue inducement. Eli Lilly used homeless alcoholics as healthy volunteers for phase I research, raising concerns about faked eligibility claims and participants' inaccurate description of side effects (14). The analysis of whether wages would be an undue inducement has several components, as explained by Macklin (4). First, people differ in their view of the importance of money. Second, people of all income groups have different levels of risk tolerance and aversion. Even though it is reasonable to assume that minimum wage may be attractive to certain groups, it may not be enough to override their risk aversion and thus would not be an undue inducement. In order to determine if a certain wage rate is an undue inducement for a particular person, such variables as their view of the worth of money, their current economic situation and their level of risk tolerance and aversion, would have to be measured. It is not clear either how to measure these variables or what weight to give them. Another partial solution to this concern would be to require testing for any condition warranting exclusion from a trial because of likely harm to the participant (13). The potential participant's word would not be sufficient if wages are to be paid. If this safeguard had been in place, Bernadette Gillcrist would have had a cardiac test before being allowed to enter the sleep trial. Such tests would raise the cost of research, but may be necessary if wages are to be offered. Furthermore, participants should not be penalized financially if they discontinue the study due to toxic side effects, since they might be tempted to underreport such side effects and put themselves at risk (15). However, financially penalizing those who leave the study for personal reasons would be allowed. In short, although concerns about the wage-payment model are valid, safeguards can be erected to minimize the potential for harm.

A final concern with the wage-payment model takes the opposite tack. According to this criticism, limiting wages to approximately the minimum wage is paternalism. Participants should be allowed to earn whatever they can (16). Ethical codes, however, have never relied solely on patient autonomy to ensure that research is ethically acceptable (17). The Nuremberg Code (18), which opens with the requirement of voluntary consent, also stipulates that research meet certain standards before it is worthy to be offered to potential participants. Requirements 2 through 8 state that every experiment must yield useful results, avoid unnecessary suffering, demonstrate an acceptable risk-benefit ratio, and be conducted by qualified persons. In the United States, IRBs are ethically mandated to assure that all of these ethical requirements are met. The whole research design, including determining the amount of payment to participants, is well within IRB purview.

Most discussions of payment for research limit their scope to nontherapeutic research, typically research utilizing healthy volunteers. Access to innovative treatments of potential therapeutic benefit is thought to be sufficient reward for participating in therapeutic research. Although phase I research with healthy volunteers is the most likely candidate for wage-payment, some therapeutic research could be included. Phase I research with potentially toxic therapies designed for life-threatening diseases, such as AIDS and cancer, where subjects are terminal patients, offers little chance of benefit (19, 20). Yet people do enter these studies hoping to personally benefit (21). Paying wages to these research participants may lower therapeutic misconception, alerting the participants to the fact that these trials are research, not therapy (8, 22).

Paying healthy volunteer and patient research participants approximately the minimum wage shows respect for their contribution to society, removes some financial barriers to research, may increase participation by those in lower socio-economic groups, and may mitigate therapeutic misconception. Any potential for such wages to be undue inducement could be minimized by such safeguards as mandatory testing for exclusionary criteria if harm might result, and not increasing payment with increasing risk.

Researchers

At present, it appears that researchers are reimbursed according to the market model. Researchers can earn more than $5,000 a subject, sometimes as much as $19,000 a subject, with bonuses for meeting a quota or for speed in recruiting. The average investigator grant has been estimated at $43,000, with some investigators earning from $500,000 to one million dollars a year (23). With such large amounts of money involved, individual cases of fraud have been uncovered (2). And there is always the danger that true informed consent may be short-circuited and eligibility criteria stretched. Dr. Robert Tenery, past chair of the Council on Ethical and Judicial Affairs for the American Medical Association, has objected to research bonuses: “Why would you get an extra $500? How can you explain that rationale? Maybe you took a patient who really didn’t need to be enrolled.” And one thoughtful IRB member has wondered, “If it is coercive to pay a patient $500, why is it not coercive to pay the clinical investigator $5,000?” (23).

To minimize the possibility of coercion for investigators, the wage-payment model should be applied to their remuneration. I propose that investigators be paid by the hour, as skilled, not unskilled, workers, at the hourly rate that an internist usually earns. Alternatively, investigators could be paid a flat fee based on an estimate of the number of hours it takes to enter and maintain a participant on a trial. This standardization would remove the undue inducement currently found in the market model of payment.

Why pay researchers at all? Because it does take time, skill and effort to recruit and maintain participants in research trials. The National Cancer Institute (NCI) reimburses the institution, not the individual investigator, $2,000 per participant enrolled in their trials. Academic investigators estimate that the true cost in these academic settings is $4,000 per participant. Furthermore, academic medicine cannot meet the demand for the number of participants needed to test new agents, with the proportion of drug studies handled by academic researchers dropping from one-third in 1990 to one-quarter in 1997. Private doctors, who (unlike many academic doctors) do not receive a salary, will need to be paid for their time.

In a wage-payment system for investigators, additional safeguards for participants would need to be established. Not only must the pay be standardized at a reasonable level, but careful control of researcher qualifications must be maintained, since instances of researchers running studies outside their areas of expertise have been reported. Training in research conduct should be required, since there is no assurance that private physicians are trained in research conduct, regulations or ethics. All investigators, both academic and private, must be routinely audited. Academic researchers have succumbed to the temptation of fame and glory (24), just as private practitioners have succumbed to the allure of big money. Only a careful audit system with “teeth” can protect us from such abuses. Finally, complete disclosure to the potential participant is the minimum requirement of any remuneration system.

Conclusions

Inducement is rampant in research. Academic researchers’ careers are built on performing successful research. Private practitioners can make significant amounts of money. I suggest that payment of money to researchers be standardized at a reasonable rate, the hourly charge of an internist, and that careful controls and audits be instituted. But if we are to pay researchers for their time and effort, we should also pay participants, with safeguards for them as well. In short, I suggest that we spread the money around.

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Panel Discussion

Audience:
This is a question about paying for risk. I'm going to pose a hypothetical situation: I set up a little hobby in which I go out into the streets of Manhattan, find competent adults, and offer them amounts of money to undertake various risks. I pay them a little bit if it's a small risk and I pay them a lot if it's a big risk. Would you curtail this activity in any way. If so, why? And if not, why not?

Dr. Rebecca Pentz:
That is an interesting question, because we actually do pay people for risk in all kinds of activities. The question is, why do we pay for risk-taking in the wage world and not in the research world? My first response is that I'm concerned that we not offer risky research to subjects in a way that would make them do things that they wouldn't normally do. For some reason, they don't understand that research is a risky enterprise and so they sign up for risky research.

Dr. Lance Stell:
One difference that occurred to me between taking risks in the wage world and in the research world is that there are a number of occupations that pay people a pretty good wage to take risks, but I think the assignment of risk in these areas is a very different kind of thing. In a job situation you can develop skills and ability with experience, so that over time the level of risk can lessen. It seems to me that in the area of medical research the subject of the research has no control. The risk is in the drugs, and there is nothing they can do to change the odds in their favor.

Audience:
Is it appropriate simply to pay people to undertake risk?

Dr. Pentz:
No it is not. It's different if you are paying them to undertake risk that also has collateral benefit to the party.

Dr. Stell:
The issues are: What risky things do we allow people to do? Do we allow them to do them and then offer them money? And, at what point does the money become too good? I don't think there is going to be a "one size fits all" answer, or a theory to explain why it is not acceptable to provide financial incentives for medically related risks, while it is okay to pay people to be stuntmen or to go down into mines where the risks can be much, much greater. I think it is a very complicated issue.

Dr. Daniel Moros:
To go even further, let's look at some of the paternalism that we practice in permitting people to assume risk. For example, we take ninth graders and praise them to the world for being good at football or being terrific wrestlers, with tremendous risk to their bodies. We could criticize the whole educational environment for the establishment of high school football. Perhaps I am blind to a value in these activities that a tremendous number of people see. I know that at one time in my life I would have outlawed high school football. I'm not sure if I would have been right to do so. It is very difficult to come to grips with the issue of what is acceptable risk and at what age.

Dr. Pentz:
Risk, as I understand it, is the probability of harm. There are two parts to it, the magnitude of the harm and the probability. Would you say that it is risky for someone to undertake an activity with a very, very small probability of death? Is that a big risk or a little risk? If we can't say what is risky, then we don't know what we are talking about.

Dr. Stell:
One particular problem with risk—and there is a lot of literature on this—is that individuals in general are very bad at assessing their own risk. A good example would be that even post-9/11, it is much, much safer to fly than it would be to drive from New York to Chicago. But most individuals aren't able to understand that, or to make that kind of informed decision very effectively. So I am generally sympathetic on the point of autonomy, but I think that we have to be careful that the risk is presented in a way that is understandable.

Dr. Moros:
In failing to honor autonomy, the IRB has failed on the consent side just as badly as it has failed on its overstatement of what constitutes improper inducement. The IRB does not inform the research subject of the Committee's risk assessment. I don't see how IRB members, in good conscience, can not tell potential subjects about the risks that concern them. The nonsense surrounding informed consents is incredible. The IRB risk analysis should be provided as part of the informed consent.

Audience:
The scandal is that except in research programs sponsored by academic medicine, subjects who accept risk associated with a research project would ordinarily be insured by the sponsoring organization. In the case of a bad outcome, they might receive some sort of compensation, maybe 1 – 2 million dollars, or more, or at least their estate would. But research institutions and egg donor institutions are playing fast and loose with people by permitting them to engage in risks. It doesn't matter how much money is offered. The sum is usually trivial compared to losing the ability to have children. And who should assess risk? Not the IRB, whose members are from our group, but insurance companies whose business it is to assess risks. They will tell you realistically the cost of the risks in running the research. I put this forth because in this discussion we keep assuming that if you inform individuals of the risk, then unless there are very strong issues of altruism, the individual will refuse to participate.

Dr. Bonnie Steinbock:
I want to remind everyone that there is a relevant distinction between magnitude and probability of risk. One could say, as a potential egg donor—yes, there is a chance that I will lose my future fertility, and that is a very big harm but a very, very small risk. If I were thirty years younger I would not be an egg donor and I would do everything in my power to prevent my daughter from becoming an egg donor. But it is not for me to say that somebody couldn't rationally understand what the risks are and agree to be a donor. Also, I don't think that the money is most manipulative here. The manipulation involves not telling donors everything they should take into account and trying to hide things from them. For example, we talked to one egg donor who said that her second cycle was cancelled and she wasn't sure why. The program had retrieved 40 eggs and she thought this meant that she was superfertile. After she left the room, the doctor said that she had been hyper-stimulated and that she hadn't been told, because they wanted her to come back in the future. He added, "Donors are very easy to manipulate."

Audience:
In terms of money, the most common problem today, particularly in academic settings, is simply the conflict of interest of being bribed. Pharmaceutical companies, medical instrument companies and others ask for expert advice, for which one is actually paid. However, those who have been paid are also the same people who sit on bodies which approve or disapprove a particular product. They are also the ones who are seen on television or might be in the newspapers promoting a product. Over the years I have been unable to persuade the medical journals to ensure that every published article, letter or editorial state whether the author has or doesn't have a conflict of interest. Readers should know if authors were taken out to dinner, sent off to Japan, etc., by somebody who influenced their opinion about what they are writing.

Dr. Lewis Burrows:
I think that whether something counts as a bribe depends on whether money is taken in exchange for the betrayal of trust. In Japan, for example, medical directors can accept up to $2,300 for their referrals, and that is not regarded as a betrayal of trust. Is this a betrayal of trust or not? I think we would quickly conclude that they are taking bribes, but that is not the way they see it. Are they wrong?

Audience:
When people have a financial interest in a center they give as much as 60% more referrals. Has anybody done an empirical study in Japan? If they get money for the referrals, do they give more referrals? If they do, I think it is a betrayal of trust even if they don't agree.

Dr. Burrows:
I don't know the answer to that, because for one thing the Japanese physicians don't talk about it. It is regarded as dishonorable to talk about. Earlier, there was a question about how successfully American physicians have disciplined their own. Disciplining can be done in private or in public. When sanctions are distributed privately, the public doesn't perceive that medicine disciplines its own.

Audience:
Going back to the question of whether it is morally permissible to donate eggs, I am trying to find an equation. We don't allow people to sell themselves into slavery even for a good cause. If I was willing to sell myself or dig anthrax out of the ground for the good of the world and a price, why would those transactions be out of bounds?

Dr. Stell:
Mill's reason for why we don't let people sell themselves into slavery is appropriate here. When you sell yourself into slavery you are giving up all of your freedom to make future choices. Mill thought that violates the principal of liberty. We don't allow you to use your liberty to destroy your liberty. I think that selling yourself into slavery is really different. It's even different from the freedom to kill yourself, where you are destroying your freedom. The dead are not going to be making any choices. If you sell yourself into slavery, you give somebody else control over your choices.

Dr. Moros:
To use Mill for the issue of slavery is one thing, but Mill was extremely opposed to paternalistic intervention.

Dr. Stell:
He would prevent people from going across an unsafe bridge. His argument was that you would be interfering with their choice but not with their best interest. Considering their best interest, they wouldn't want to cross an unsafe bridge.

Audience:
That would be equivalent to prohibiting women from selling eggs without being told everything.

Dr. Steinbock:
But what you can do is tell them. What I think should be done, particularly in terms of surrogacy, is that the surrogate should have a lawyer who is representing her interests, so that she is both being informed and having someone protect her. What happens now with surrogacy to some extent, but even more commonly with egg donation, is that young woman think they are being taken care of by the lovely people at the clinic who are being so nice to them. They don't understand the conflict of interest. The interest is all about wanting to get as many eggs as possible for the people who are to receive them. What you have to do is change the institutional structure to assure that people are protected. Focusing on money keeps us from looking at other things which are much more significant.

Audience:
Even when you sell a car there are certain standardized disclosures that have to be made. You are describing a situation where the most rudimentary standard disclosures are not being made. But, does that mean the procedure shouldn't be done?

Audience:
In living liver donor transplantation, I believe there have been one or two deaths, which amounts to a 1% or lower risk of death. As a surgeon, do you think that is too much of a risk of death to allow anybody to undertake voluntarily or for money?

Dr. Burrows:
For the time being, I asked for a moratorium, despite the fact that it might upset my colleagues in the transplant field. Not only because there is a risk of death, but because there is also risk for major complications, prolonged hospitalization, and lots of side effects. Only centers with the requisite proficiency should do the operation. I asked for a moratorium because I think that even a 1% risk of death is too high. There is only one place in the country that is doing living donor pancreas transplants, and that's in Minnesota. The exact figure hasn't been disclosed, but it involves a 10 – 15% chance of the donor eventually developing diabetes. I think that is an unnecessary risk, and I would put a moratorium on that for sure. Liver donation is truly a life-saving operation. The recipients who get the livers would die within a year or sooner without them. But again, I think the procedure should be in the hands of the most competent transplant people before we extend it, as we have with kidney transplant.

Audience:
So what you are pointing to here is another distinction that people don't usually want to make. People like treating all of these professionals as being equally professional, and you are recognizing huge differences. We don't like making distinctions about money and we don't like making distinctions about expertise, but they are all relevant.

Early Reactions to Harvey's Circulation Theory:

The Impact on Medicine

Steven A. Lubitz, M.D.

Abstract

In early 17th century Europe, scientific concepts were still based largely on ancient philosophical and theological explanations. During this same era, however, experimentation began to take hold as a legitimate component of scientific investigation. In 1628, the English physician William Harvey announced a revolutionary theory stating that blood circulates repeatedly throughout the body. He relied on experimentation, comparative anatomy and calculation to arrive at his conclusions. His theory contrasted sharply with the accepted beliefs of the time, which were based on the 1400-year-old teachings of Galen and denied the presence of circulation. As with many new ideas, Harvey's circulation theory was received with a great deal of controversy among his colleagues. An examination of their motives reveals that many proponents agreed with his theory largely because of the logic of his argument and his use of experimentation and quantitative methods. However, some proponents agreed for religious, mystical and philosophical reasons, while some were convinced only because of the change in public opinion with time. Many opposed the circulation theory because of their rigid commitment to ancient doctrines, the questionable utility of experimentation, the lack of proof that capillaries exist, and a failure to recognize the clinical applications of his theory. Other opponents were motivated by personal resentments and professional "territorialism." Beyond the immediate issues and arguments, however, the controversy is important because it helped establish use of the scientific method.

Key Words: William Harvey, circulation, medical history, scientific method.

In 1628, the English physician William Harvey (1578–1657) published his *Exercitatio anatomica de motu cordis et sanguinis in animalibus (Anatomical studies on the motion of the heart and blood)*. Using experimentation, comparative anatomy and calculation, he startled the scientific world by demonstrating that the heart circulates blood repeatedly throughout the body (Fig. 1) (1).

As with many new theories, Harvey's was controversial because it clashed with the leading dogmas of the time. Brimming with inconsistencies (1, 2), the governing doctrine concerning the heart and blood was based on the teachings of the ancient Greek physiologist Galen and had sufficed for more than 1400 years. Galen taught that food traveled to the liver, where it was transformed into blood (Fig. 2). Veins emanating from the liver carried blood throughout the body; some of these veins crossed through septal pores from the right to the left ventricle. Galen claimed that venous blood nourished the lungs—but no pulmonary circuit was recognized. Inhaled life-sustaining "spirits" supposedly mixed with blood in the left ventricle, where together they were expelled into the arteries by the innate heat of the heart. With the single exception of pores in the interventricular septum, there was no mention of a communication between arteries and veins (2, 3). (Capillaries were discovered in 1660 by Marcello Malpighi [3]).

Although some people knew of the pulmonary circulation and one-way valves (2, 3), it is fair to conclude that the function of the heart, blood, and vasculature was largely misunderstood prior to Harvey. Given this environment of confusion, it is not surprising that Harvey's claims received so much criticism. Surely Harvey had anticipated this, since in chapter 8 of

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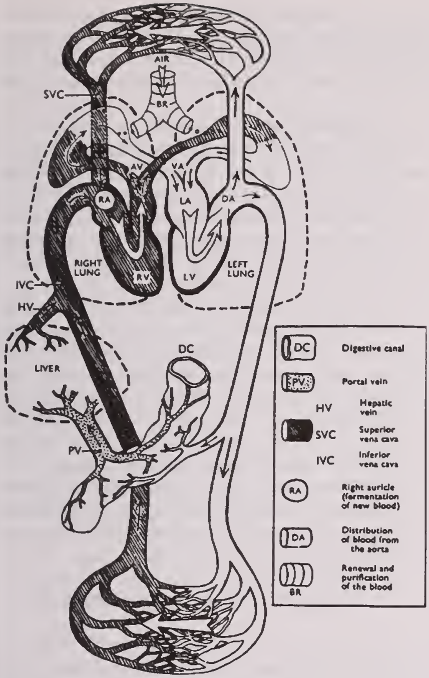
AIR
SVC
BR
RA
AV
VA
LA
DA
RIGHT LUNG
RV
LV
LEFT LUNG
IVC
HV
LIVER
DC
PV
DC Digestive canal
PV Portal vein
HV Hepatic vein
SVC Superior vena cava
IVC Inferior vena cava
RA Right auricle (fermentation of new blood)
DA Distribution of blood from the aorta
BR Renewal and purification of the blood

Fig. 1. The circulatory system of the blood as taught by William Harvey in the 17th century. RV, LV: right and left ventricles, respectively. Reproduced with permission, from Chauvois L. William Harvey: his life and times, his discoveries, his methods. New York: Philosophical Library; 1957 (21).

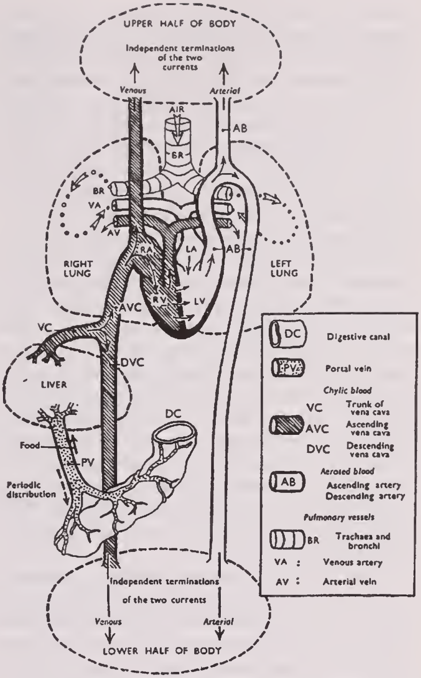
UPPER HALF OF BODY
Independent terminations of the two currents
Venous
Arterial
AIR
AB
BR
BR
VA
AV
RA
LA
AB
RIGHT LUNG
LEFT LUNG
RV
LV
AVC
VC
DVC
LIVER
DC
Food
PV
Periodic distribution
Independent terminations of the two currents
Venous
Arterial
LOWER HALF OF BODY
DC Digestive canal
PV Portal vein
Chylic blood
VC Trunk of vena cava
AVC Ascending vena cava
DVC Descending vena cava
Aerated blood
AB Ascending artery Descending artery
Pulmonary vessels
BR Trachaea and bronchi
VA : Venous artery
AV : Arterial vein

Fig. 2. The traditional system of the movements of blood as taught by Galen in the 2nd century A.D. RA, LA: right and left auricles, respectively. Reproduced with permission, from Chauvois L. William Harvey: his life and times, his discoveries, his methods. New York: Philosophical Library; 1957 (21).

De motu cordis he even admitted the depth of his fears should his doctrine be ill-received (1):

> What remains to be said on the quantity and source of the transferred blood, is, even if carefully reflected upon, so strange and undreamed of, that not only do I fear danger to myself from the malice of a few, but I dread lest I have all men as enemies, so much does habit or doctrine once absorbed, driving deeply its roots, become second nature, and so much does reverence for antiquity influence all men.

Many of Harvey's most accomplished peers challenged his theory. Now that his model has survived for almost 400 years as the key to understanding much of physiology, disease and therapy, one might ask, what influenced his critics? Why did his advocates support him, and why did his adversaries oppose his new idea? In this paper, I will identify common motives that influenced some of Harvey's most prominent critics within the scientific community during his lifetime. Yet this controversy may be worth a closer look for reasons that transcend the immediate issue of Harvey's new theory. For the episode also marks the birth of modern medical science.

Proponents — Experimentation and the Scientific Method

Four centuries ago, scientific investigation hardly resembled that of today. In Europe, mysticism played a legitimate role in scientific rationale (4) and astrology was a required subject at some medical schools. Investigation was unstructured, and eloquent theory sufficed as proof for new doctrines (5). It was in 1620 that Francis Bacon first described inductive reasoning—the basis of the scientific method that guides research today (3, 6). Of course, scientists had utilized experimentation long before Harvey, Galen among them. Yet its prominence had waned for centuries, and it did not begin to reemerge from its long eclipse until the late 1500s, with the efforts of investigators like Andreas Vesalius and Galileo Galilei (3, 7).

With *De motu cordis*, Harvey set a new standard of investigation by employing experimentation and quantitative reasoning to defend his theory (2, 3, 8). In chapter 9, he used volumetric measurements to calculate the cardiac output. This was the cornerstone of his argument, as he reasoned that in the absence of circulation, the quantity of ingested food alone was not enough to account for the total cardiac output during several minutes or longer; this output far exceeded the blood volume of the body. This rationale, together with the knowledge that valves prevent retrograde bloodflow in veins, enabled Harvey to conclude that blood must circulate (1).

The logic of Harvey's theory impressed many in the medical community (9–11). Yet the most compelling aspect of his argument was his use of experimentation, due to its reproducibility. Using autopsy and vivisection, many of Harvey's colleagues became vocal supporters. Among them were Johannes Walaeus (9), Herman Conring (10), Andrea Argoli (11), Johan Vesling (12), Henry Power (13) and Fortunatus Vopiscus Plemp (10).

Plemp's case illustrates the impact of experimental evidence in this debate. Plemp, a medical professor in Louvain who initially opposed the circulation theory, ironically converted while challenging one of Harvey's adherents, Rene Descartes (10). Descartes, a mathematician and philosopher, read *De motu cordis* and declared his approval in *Discourse on method* (1637), with some modifications (14). In *Discourse*, Descartes rejected Harvey's notion of forceful systole. Instead, he explained that "natural heat implanted by God in the heart" caused blood to vaporize and expand, resulting in diastole. This vaporization then propelled the blood forward, "...causing all the branches of the arterial vein [pulmonary artery] and the grand artery [aorta] to swell almost at the same time as the heart. Immediately after, the heart deflates as do these arteries, because the blood that has entered them has grown cold" (14).

As intricate as Descartes' arguments were, they lacked the support of experimental evidence (12). Furthermore, he incorrectly concluded that blood is ejected at the peak of ventricular diastole.

Descartes sent a copy of his *Discourse* to Plemp. Plemp responded, challenging his claims on the heat of the heart and vaporization of blood. This disagreement enticed Plemp to investigate the matter firsthand, employing vivisection. Plemp's observations disproved Descartes' claims, and he became an adherent of Harvey's doctrine (10).

In the years following publication of *De motu cordis*, medical schools began to accept the practice of anatomical investigation (15). This acceptance of experimentation and anatomical study may well be Harvey's greatest contribution to the scientific method. Interestingly, it was achieved predominantly by Harvey's followers as they attempted to duplicate his findings and conclusions. Their meticulous attempts to replicate his experiments spawned new experiments, and they thereby perpetuated his investigatory style (7, 15).

Proponents — Eccentric Rationale

As exampled by Descartes and Plemp, proponents accepted Harvey's theory for varying reasons. Furthermore, despite the praise afforded to Harvey for his use of experimentation and quantitative methods, many agreed with him for reasons other than those set forth in *De motu cordis*.

Robert Fludd, a friend of Harvey and a fellow London physician, wrote the first published acceptance of the circulation theory (12). Fludd was an active member of the Rosicrucians, a religious movement based on mystical tenets. He turned to the cabalistic principles of polarity and angels to explain the expansion and contraction of the vessels (4). Fludd also relied on astrology and alchemy to explain phenomena, and likened the circulation of blood to the orbits of the cosmos (16). His approval of Harvey's theory, while enthusiastic, has been attributed to the fact that it affirmed his own mystical views on circular motions (12, 16).

Still, Harvey's theory gained popularity through such writings. In 1611, Caspar Bartholin wrote a very successful textbook of anatomy, *Institutiones anatomicae*. Ultimately, his son, Thomas Bartholin, wrote a new edition of the book containing accounts of recent discoveries, including that of circulation. With this new edition (9), he has been credited with "publish[ing] in 1641...the first textbook containing an exposition of Harvey's doctrine," through which he "introduced Harvey's doctrine into Denmark."

However, it wasn't until a later edition, published in 1651, that Thomas Bartholin actually conceded the existence of circulation. Moreover, his beliefs continued to differ significantly from Harvey's. Bartholin argued that the interventricular septum was permeable, and he was reluctant to classify the heart as a muscle (9). Medical historian Roger French suggests that Bartholin was influenced by an unwillingness to disturb the reputation of his father's text, and by his uncle, Oluff Worm, an adherent of ancient doctrine who opposed the concept of circulation. In fact, according to French (10):

> ...Bartholin never fully accepted a Harveian position.... In essence, Bartholin waited until he saw that the circulation controversy was almost settled in Harvey's favor before accepting, because so many others were doing so, that it represented truth. Then it became important for him to weave it into his textbook.

Like Bartholin and Descartes, other proponents accepted Harvey's theory only with modifications. For example, Franciscus Sylvius believed that food, converted and transported to the heart in the form of chyle, was transformed into blood via the "fire" of the right ventricle. As French argues, the reason many of these individuals agreed with some aspects of Harvey's theory and disagreed with other aspects, was that they had different natural philosophies (10).

Opponents

As was the case among proponents, Harvey's opponents also had various reasons for disagreeing with his theory. James Primrose, an indefatigable critic, published a dissent to *De motu cordis* in 1630 containing numerous objections commonly voiced by Harvey's opponents. He argued that the doctrine was a "novelty" and only served to "destroy" traditional medicine. Furthermore, he maintained that circulation would be detrimental in conditions such as fever, by repeatedly and inappropriately delivering "putrid" material to the entire body. Primrose even took aim at the backbone of Harvey's argument, objecting that his calculation of cardiac output was too variable from beat to beat (10). Primrose's aversion to experimentation, however, left him without evidence to support his criticisms (10, 17, 18).

Author Geoffrey Keynes contends that Primrose simply was "congenitally unable to accept new ideas" (12). While this statement reflects the frustration experienced by historians regarding Primrose's obstinacy in rejecting the theory of circulation, it does not address his motives. Primrose was raised in France and ultimately moved to England. When he joined the College of Physicians in London in 1629, Harvey was one of his examiners. At that time, foreigners, regardless of qualification, were prevented from becoming more than licentiates in the College (19). Nonetheless, Primrose soon persuaded the king to permit him to lecture on medicine in public, an appointment the college reacted to with embarrassment (12). They forced him to stop lecturing, explained that he was unqualified because he was merely a licentiate (10), and barred him from candidature in the college. This struggle for acceptance into the college, as well as the presence of Harvey as one of his initial examiners, may be one reason why Primrose adopted such vehement opposition to Harvey's theory (19).

It is interesting to note that, despite Harvey's membership and committed involvement in the college, his theory was not entirely embraced by its members. During the early 17th century, the College of Physicians served the purposes of protecting its members and monopolizing the practice of medicine by fending off competitors, such as surgeons and apothecaries (5, 10, 19). Physicians traditionally were educated differently than their competitors, with much teaching focused on the principles propagated by Hippocrates and Galen. The college learned to exploit this difference, citing such knowledge as a requisite for proper training. Thus, the college became heavily invested in the classical teachings (5). In fact, fines could be imposed upon practitioners who veered from the teachings of this "rational medicine" (10). Pressure to adhere to classical doctrine is evidenced by the fact that some teachers of anatomy failed to address Harvey's theory altogether (10, 12). Moreover, twelve years after *De motu cordis* was published, the president of the college, in front of Harvey, neither approved nor condemned one candidate's thesis because it promoted circulation (12). French goes so far as to suggest that perhaps Harvey had *De motu cordis* printed overseas for fear of preaching unorthodox views at home (10).

Adherence to ancient doctrine extended beyond England, as evidenced by Caspar Hofmann, a professor of medicine at the University of Altdorf in Germany. During Harvey's trip to continental Europe in 1636, Hofmann agreed to observe a public experiment at which Harvey was to demonstrate proof of circulation. Hofmann promised to reveal his opinion after he had seen the demonstration. The experiment ensued on May 19, but Hofmann remained unconvinced (20).

Historians have had difficulty citing reasons for Hofmann's opposition. On the day of the experiment, Hofmann wrote a short letter to Harvey in which he gave little explanation to justify his disagreement, other than to say ambiguously that circulating blood implied nature's futility in "abound[ing] in unnecessary things" (20). Hofmann disagreed with Harvey because he did not see the purpose of circulation, and believed that such a process would "re-cook" the blood and convert it to bile. Furthermore, by calculating cardiac output, Harvey may have "tried to quantify the unquantifiable," in Hofmann's mind. Hofmann believed that blood became "ebullient" in the heart, and therefore felt it was impossible to accurately measure the volume of blood in or expelled from the heart at any given time. Like others, Hofmann also was troubled by Harvey's lack of evidence of any arteriovenous anastomoses (2, 9, 20). Thus, Hofmann rejected circulation because he opposed Harvey's quantitative evidence, lacked proof of the existence of capillaries, and was committed to a traditional but erroneous conception of cardiovascular physiology.

Opposition to Harvey's new ideas, while persistent, was actually fairly mild, in large measure because he avoided any theological implications in his conclusions. Some 75 years earlier, in 1553, Spanish physician and theologian Michael Servetus had described the pulmonary transit of blood in his publication *Christianismi restitutio* (21). However, his work was basically a theological treatise that challenged traditional religious beliefs; it offended Catholics and Protestants alike (22). Fleeing from the Inquisition in France, Servetus came to Geneva, Switzerland, where John Calvin, the Protestant reformer, having read his book, had him arrested and burnt at the stake. Most copies of the book were soon destroyed (21). Had Servetus been able to separate religion from science, it is possible that his discovery of the pulmonary circulation would have been recognized and appreciated.

As it was, Servetus' discovery remained unknown to Harvey (2). *De motu cordis* did not arouse comparable opposition from the Church of England, perhaps because the work was virtually devoid of religious references. Yet this very lack of religious references appears to have motivated at least one of Harvey's critics. Emilio Parigiano, a respected member of the Venetian College of Physicians, criticized the circulation theory for a number of reasons. As a devout Christian, Parigiano maintained a generally theological interpretation of phenomena. He believed Harvey's naturalistic account of the circulation to be misguided because it failed to incorporate a divine rationale for such a system (10). Moreover, Harvey derived much of his analytical approach from the teachings of Aristotle, a polytheist. To Parigiano, this "promotion" of Aristotelian views may have made Harvey's ideas especially objectionable (8).

Given the conventions of the time, it is understandable that Harvey's experiments were greeted with suspicion. Parigiano, among others, opposed the process altogether. He argued that Harvey had been misled by drawing conclusions from the anatomy of animals. Not only were animals "imperfect" creatures that were "distant" from man, but Harvey's experiments were unnatural, failing to replicate the actual functions of the parts as they existed in nature (10):

> Good God! Is this a valid mode of experience, when the hearts of these creatures have been torn from their bodies, exposed to the air, lacerated, and are lying exhausted and half dead on the table or in the hand, devoid of blood and spirits?

"Territorialism" may also have been a factor in Parigiano's rejection of Harvey's ideas. Although the College in London did not uniformly endorse Harvey's theory, it may have appeared that way to Parigiano. Given his loyalty to the Venetian College of Physicians, he may have been offended by Harvey's address of *De motu cordis* to "Doctor Argent, the excellent and accomplished President of the Royal College of Physicians [in London], and...his esteemed colleagues" (1). Simply put, his rejection of the doctrine may have been partly due to his fear that the authority of the Venetian College of Physicians was threatened by its counterpart in London (10).

Harvey's most ardent opponent was Jean Riolan, a distinguished anatomist from Paris, and a teacher of Primrose. Riolan challenged *De motu cordis* in his *Opuscula anatomica nova* (1649) (23). As a prominent teacher, dean of the Medical Faculty in Paris, the son of a physician, and himself physician to Marie de Medici, Riolan was professionally invested in the ancient doctrines to which he had subscribed and which he had taught throughout his career (10, 17, 24). As a teacher and dean, he was entrusted with propagating these conservative teachings for reasons similar to those of the College of Physicians in London (10).

Ultimately, Riolan proposed his own circulation theory. In deference to antiquity, he still maintained that blood was produced in the liver, the interventricular septum was permeable, and pulmonary circulation did not exist. Although he conceded some movement of blood from arteries to veins in the periphery, he denied any flow of blood through the abdominal organs and argued that only a few drops of blood were expelled from the heart with each beat (17). As with others, Riolan's arguments lacked experimental backing. Like Bartholin, Riolan may have conceded some form of circulation only because of the changing consensus among his peers (10).

In the search for common motives affecting the reception of Harvey's doctrine, it is difficult to miss the striking differences in age between his supporters and opponents. Other authors have referred to this phenomenon as well (9, 11, 12). Both Weil (25) and Keynes (12) have provided valuable lists of Harvey's critics during his lifetime. The vast majority of supporters were 40 years of age or younger in 1628, the year *De motu cordis* was published. Conversely, virtually all the opponents were older than 40 at the time of publication. Notable exceptions include Fludd and Argoli, both supporters, aged approximately 54 and 58 years, respectively, in 1628. Primrose, a critic, was about 30 years old. So it may not have been age per se as much as relative openness to new ideas and methods that distinguished Harvey's supporters from his opponents. New ideas were in the air, in the early 1600s, for those willing to learn.

Summary of Motives

Other than their relative youth, factors common among Harvey's proponents included a willingness to do firsthand experimentation and an openness to quantitative evidence and the scientific method. However, religious and mystical beliefs also played important roles for some proponents, despite Harvey's lack of reference to such beliefs in *De motu cordis*. Lastly, we see that shifting public opinion probably convinced at least some who were otherwise reluctant to accept the new theory.

Harvey's opponents were often heavily invested in ancient doctrine, and may have feared professional repercussions by accepting the circulation theory. Some simply felt there was a lack of clinical application of this new theory. Others disagreed because they saw no evidence of a connection between arteries and veins through which blood could return to the heart. Ironically, some were altogether opposed to experimentation, largely considered today the most convincing component of Harvey's argument. Still other critics were motivated by religion, professional territorialism, and personal resentments.

Conclusion

Among Harvey's critics, there were various motives for agreeing or disagreeing with his ideas. While there were common motives within each group, by no means were all proponents, for example, united in their arguments for the new doctrine. Motives varied, and at times proponents even disagreed with one another. Since its publication, scrutiny of *De motu cordis* has allowed us to confidently accept Harvey's revolutionary doctrine as the basis for the modern understanding of human anatomy and physiology. We have both Harvey and his proponents to thank for this. However, we must also thank his critics, for as a result of their challenges, members of the scientific community began to embrace experimentation and accept the scientific method, to evaluate his doctrine. These serve as the two pillars of today's attempts to understand the biological basis of medicine. Few controversies have proved more fertile or influential in shaping the future.

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Evaluation of Serum Anion Gap in Patients with Liver Cirrhosis of Diverse Etiologies

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Abstract

Background: The low serum anion gap (AG) in patients with hepatic cirrhosis is generally attributed to hypoalbuminemia. Serum immunoglobulin G (IgG) (elevated in chronic viral hepatitis) and IgA (elevated in alcoholic cirrhosis) have different isoelectric points, and thus may affect serum AG in opposite directions.

Aim: To define the normal serum AG in patients with liver cirrhosis of diverse etiologies.

Study design: We retrospectively compared serum AG of 144 stable cirrhotics and 286 control patients (consecutive hospital admissions with serum creatinine concentration < 2 mg/dL).

Results: Serum AG was significantly lower among the cirrhotics, compared to the controls (5.8 ± 2.2 mEq/L vs. 7.0 ± 2.2 mEq/L, respectively, $p<0.005$). However, when patients with serum albumin concentration < 3.5 g/dL were excluded, there was no significant difference between the cirrhotics vs controls (6.7 ± 1.8 mEq/L vs. 7.0 ± 2.2 mEq/L, p=ns). Moreover, patients with liver cirrhosis secondary to chronic viral hepatitis had AG similar to that of the alcoholic cirrhotics (5.6 ± 2.5 mEq/L vs. 6.0 ± 1.9 mEq/L, p=ns). There was a positive correlation between serum albumin concentrations > 1.9 g/dL and serum AG, and a tendency toward an inverse correlation between serum globulin concentration and serum AG.

Conclusion: Our results support the contention that hypoalbuminemia accounts for the decreased serum AG frequently observed in patients with liver cirrhosis. We found no difference in serum AG with different causes of cirrhosis. We also suggest a lower reference range for normal serum AG.

Keywords: Anion gap, acidosis, cirrhosis, acid-base.

Introduction

THE SERUM ANION GAP (AG) has traditionally received attention as a valuable clinical tool to assess acid-base status (1), and has acquired an important role in the differential diagnosis of metabolic acidosis (2) The disorders marked by a decrease in serum AG have received less attention than those associated with an increase in AG, because downward deviation occurs less often and is associated with less acutely life-threatening conditions.

Patients with liver cirrhosis have a polyclonal increase in immunoglobulins (IG) due to decreased degradation (3, 4) in the face of normal or increased synthesis of immunoglobulins. IgG paraproteins have isoelectric points (Pi) > 7.4 and therefore are positively charged at normal serum pH. It has been shown that a substantially increased level of IgG is associated with a decrease in serum AG (3, 5, 6). In contrast, the Pi of IgA is < 7.4; thus, at normal serum pH, it is more anionic, which would be expected to expand the serum AG. While patients with cirrhosis secondary to chronic viral hepatitis may have high serum IgG levels, those with cirrhosis due to alcoholic hepatitis are known to have high serum IgA levels (7). Thus, serum AG in these two groups of patients would be expected to be different.

Another feature of liver cirrhosis is hypoalbuminemia. Albumin is responsible for ~75% of the serum AG (8). Each 1 g/dL reduction in serum albumin concentration is associated with

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~2.5 mEq/L reduction in serum AG (9). Hypoalbuminemia is suggested to be the most likely explanation for the decrease in serum AG in cirrhotics (4).

In the present study, we compare the serum AG of 286 consecutive hospital admissions (controls) whose serum creatinine concentrations were < 2 mg/dL with serum AG of 144 stable patients who had biopsy-proven liver cirrhosis. We also compared the serum AG of cirrhotic patients with the diagnosis of chronic viral hepatitis with the serum AG of cirrhotic patients who had ethanol abuse.

Patients and Methods

We retrospectively analyzed the routine serum electrolytes and calcium, phosphorus, magnesium and albumin concentrations of 144 stable patients with biopsy-proven liver cirrhosis, who were being followed in the hepatology clinic at Saint Louis University Health Sciences Center. The mean (± SD) age of the patients was 53 ± 10 years. Eighty-seven patients were male and 57 were female. The etiologies of liver cirrhosis were as follows: chronic viral hepatitis (hepatitis B or C) in 83, ethanol abuse in 18, cryptogenic cirrhosis in 19, primary sclerosing cholangitis in 7, alpha-1-antitrypsin deficiency in 5, primary biliary cirrhosis in 3, nonalcoholic steatohepatitis in 3, autoimmune hepatitis in 2, sarcoidosis in 2, methotrexate hepatotoxicity in 1, and liver transplant failure in 1. For the control group we used 286 consecutive admissions to the hospital, during the same time period, whose serum creatinine concentrations were < 2 mg/dL. The mean age of the control group was 52 ± 18 years. Serum AG was calculated as serum concentrations of Na^+ - (Cl^- + HCo_3^-). Serum electrolytes, tCO_2 and calcium concentrations were measured using ion specific electrodes (Beckman Synchron CX7 Clinical System Autoanalyzer, Brea, CA). Serum albumin concentration was measured by dye binding method using bromcresol-purple photometries. Serum PO_4 concentration was measured by ultraviolet (UV) reduction method using phospho molibdate UV.

Statistical Analysis

The data is expressed as mean ± SD. An unpaired student t-test was used to compare the difference between the groups ($p < 0.05$ was considered significant).

Results

The concentrations of serum AG, tCO_2, albumin, globulin, calcium, phosphate and magnesium for the control group, all cirrhotic patients, cirrhotics due to chronic viral hepatitis (hepatitis B or C), cirrhotics due to ethanol abuse, and cirrhotics who had serum albumin concentration > 3.5 g/dL are shown in the table. The serum AG among all cirrhotics as a group was significantly lower than in the control group (5.8 ± 2.2 vs. 7.0 ± 2.2, $p<0.005$). However, when we excluded cirrhotics with serum albumin concentration < 3.5 g/dL, there was no significant difference between cirrhotics with albumin > 3.5 g/dL vs. control (6.7 ± 2.2 vs. 7.0 ± 2.2, p=ns). The patients with cirrhosis sec-

TABLE

Comparison of Serum Anion Gap, Bicarbonate, Albumin, Globulin, Calcium, Phosphate and Magnesium among Different Groups

	n	**AG mEq/L (range)**	**tCO_2 mEq/L (range)**	**albumin g/dL (range)**	**globulin g/dL (range)**	**Ca mg/dL (range)**	**PO_4 mg/dL (range)**	**Mg mg/dL (range)**
Control	286	7.0±2.2 (2.0 – 12.0)	25.9±3.0 (14.0 – 36.0)	4.0±0.3 (1.3 – 4.9)	3.0±0.6 (1.4 – 6.0)	9.6±0.4 (8.6 – 10.5)	3.6±0.7 (1.9 – 5.6)	-
All cirrhotics	144	5.8±2.2* (0.0 – 13.0)	25.6±3.4 (4.1 – 32.0)	3.4±0.6* (1.4 – 4.7)	3.6±0.8* (1.9 – 5.4)	9.0±0.6 (6.4 – 10.8)	3.4±0.8 (1.6 – 7.2)	2.0±0.3 (1.5 – 4.0)
Cirrhotics (Hepatitis B/C)	83	5.6±2.5* (0.0 – 13.0)	25.4±3.6 (4.1 – 32.0)	3.4±0.6* (1.7 – 4.5)	3.7±0.7* (1.9 – 5.3)	9.0±0.7 (6.4 – 10.8)	3.4±0.9 (1.8 – 7.2)	2.0±0.3 (1.5 – 4.0)
Cirrhotics (Ethanol)	18	6.0±1.9 (3.0 – 10.0)	25.5±3.4 (20.0 – 31.0)	3.3±0.7* (2.0 – 4.7)	3.7±0.8* (2.3 – 4.7)	9.0±0.6 (8.2 – 9.7)	3.6±0.7 (2.1 – 4.8)	2.1±0.4 (1.6 – 2.7)
Cirrhotics (albumin≥3.5)	65	6.7±1.8 (2.0 – 13.0)	26.8±2.1* (22.0 – 32.0)	3.9±0.3 (3.5 – 4.7)	3.5±0.7* (2.3 – 4.8)	9.4±0.4 (8.5 – 10.6)	3.5±0.8 (1.6 – 7.2)	2.0±0.2 (1.6 – 2.7)

AG = anion gap; data presented as mean ± SD (range); * $p<0.05$ vs. control

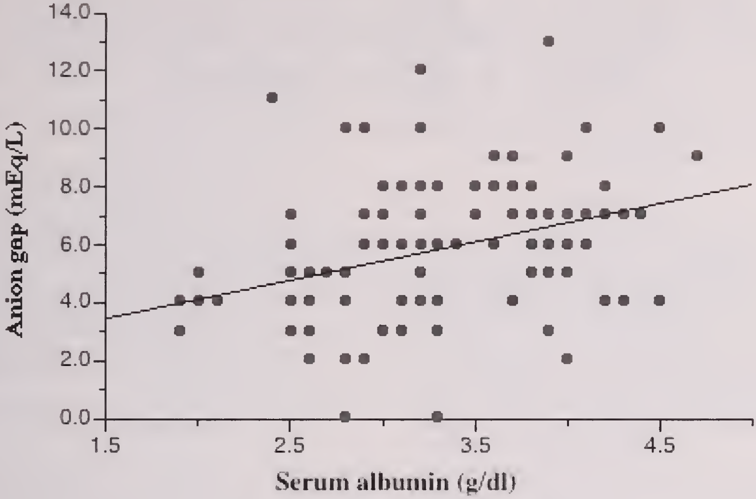

Figure. There was a positive correlation between serum AG and serum albumin concentrations > 1.9 g/dL ($r^2 = 0.2$, p=0.0001).

ondary to chronic viral hepatitis had a lower serum AG than those with cirrhosis due to ethanol abuse, but the difference did not reach statistical significance (5.6 ± 2.5 vs. 6.0 ± 1.9, p=ns). Serum AG showed a positive correlation with serum albumin concentrations > 1.9 g/dL ($r^2 = 0.2$, p=0.0001, Figure), whereas there was an inverse correlation, though statistically not significant, with serum globulin concentration (p=ns).

Discussion

Serum AG is widely used in the evaluation of metabolic acidosis (1). A low serum AG is found in IgG multiple myeloma (5); hypoproteinemia (10); severe hyperkalemia, hypercalcemia and hypermagnesemia; and cases of acute lithium poisoning (11) or the use of other cationic drugs (12). Recently, the reference range for normal serum AG has undergone a downward shift from 12 ± 4 mEq/L (1) to 3 – 11 mEq/L, which is reflective of the current methods of measuring serum sodium, chloride and bicarbonate concentrations with modern ion-selective electrode technology (13). The anions normally present in serum include anionic proteins (albumin, and to a lesser extent, alpha and beta globulins), sulfate, phosphate and organic anions. Albumin is the most abundant anionic serum protein and is estimated to be responsible for ~75% of the serum AG (8). The synthetic function of liver is substantially affected in cirrhosis; thus, serum concentrations of albumin and other proteins synthesized in the liver (i.e., most of the alpha-1, alpha-2 and beta globulins) are markedly diminished. Therefore, cirrhotics tend to exhibit a low serum AG, which is often attributed to hypoalbuminemia (4). However, patients with cirrhosis also have higher serum concentrations of immunoglobulins. The elevated serum IgG concentrations seen in patients with chronic viral hepatitis may theoretically decrease serum AG (due to its Pi > 7.4), while the elevated serum IgA level seen in patients with alcoholic cirrhosis would be expected to expand serum AG (due to its Pi < 7.4).

In the present study we found that serum AG is significantly lower in cirrhotics as compared to the controls. However, when corrected for serum albumin concentration > 3.5 g/dL there was no significant difference. We also found a positive correlation between serum AG and serum albumin concentrations. On the other hand, we found an inverse, though insignificant, correlation between serum AG and serum globulin concentrations. Serum AG was slightly lower among patients with cirrhosis secondary to chronic viral hepatitis than among those with cirrhosis secondary to ethanol abuse, but the difference did not reach statistical significance. That is, we found no significant difference in serum AG with different causes of liver cirrhosis (i.e., chronic viral hepatitis vs. ethanol abuse). In addition, we suggest a lower range for normal serum AG (7 ± 2; range 2.0 – 12.0 mEq/L) as was recently suggested (13).

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Compression of the Radial Branch of the Median Nerve Due to an Anomalous Muscle Belly of the First Lumbrical in a Child

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Abstract

Compression of the radial branch of the median nerve due to an anomalous muscle belly of the first lumbrical is a new diagnostic entity. We found this in the case of a 12-year-old girl with intermittent pain, weakness and paresthesias in the right hand. Provocative signs and symptoms in the distribution of only the radial branch of the median nerve are the most important signs distinguishing this case from carpal tunnel syndrome.

Key Words: Compression, median, nerve, lumbrical, pediatric.

Case Report

A 12-YEAR-OLD, RIGHT-DOMINANT female patient complained of 1 1/2 years of intermittent pain, weakness and paresthesias in the right hand within two minutes of beginning to write, play the cello, or play the piano. Specifically, the paresthesias, weakness and pain were in the radial side of the index finger and thumb. Fifteen months before, she had had a "lesion" removed from the dorsum of the first metacarpophalangeal joint, a procedure that was meant to alleviate the above-mentioned symptoms. Before the operation, she and her parents saw no mass, but her sensitivity to range of motion of the thumb was temporarily diminished after the surgery and during four weeks of immobilization. Otherwise, her symptoms persisted.

On physical examination, she had a painless 1 cm transverse scar over the dorsum of the first metacarpophalangeal joint. Wrist compression sign was positive to the radial 1 1/2 digits. In this test the examiner's digit compresses the median nerve at the distal flexion crease of the palm for less than 30 seconds. A positive response includes reproduction of the patient's symptoms in the sensory distribution of the median nerve, which normally includes the radial 3 1/2 digits. Pressure over the radial branch of the median nerve at the distal-lateral edge of the transverse carpal ligament reproduced her symptoms, as did writing for less than a minute, holding a bottle, or grasping the bow of her cello and playing, as she demonstrated.

X-rays of the hand and wrist showed no bony or soft tissue abnormalities. Magnetic resonance imaging (MRI) of the hand and wrist depicted thickening of the flexor tenosynovium within the carpal tunnel. At the time of surgery, the carpal tunnel was entered and the transverse carpal ligament incised, more radially than usual, due to the location of the patient's Tinel's sign. With the index finger extended, an elongated, anomalous hypertrophied first lumbrical was found (Fig. 1). Originating, as it normally does, from the index profundus tendon, its tendinous origin was found to extend from the distal forearm rather than from the area of the distal transverse carpal ligament. Its insertion into the lateral band at the proximal phalanx was not visualized, but was demonstrated by its passive action. The lumbrical's greatest diameter lay dorsal to the radial branch of the median nerve at the distal radial edge of the transverse carpal ligament. To approximate the adjacent lumbrical in size, the portion of this elongated muscle that lay within the carpal tunnel and distal forearm was excised (Fig. 2).

Postoperatively, the patient's preoperative symptoms disappeared. Six months postoperatively, she still had some symptoms of pillar pain. At 1 1/2 years, the pain was gone.

Discussion

Children have been found to have carpal tunnel syndrome due to idiopathic thickening of the flexor tenosynovium; congenital anomalies of the lumbricals, carpal tunnel, and sublimi;

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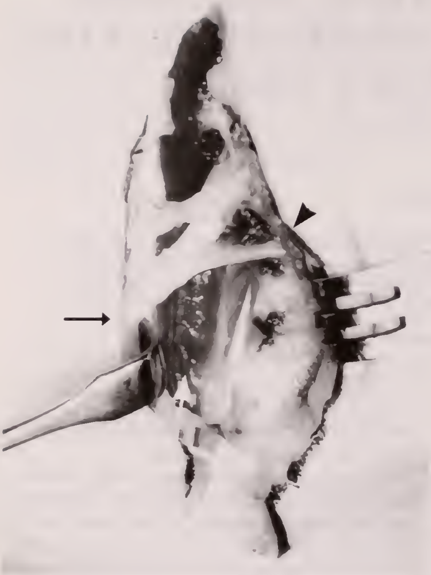

Fig. 1. The transverse carpal ligament has been sectioned and retracted with the skin. The first lumbrical muscle was seen on the floor of the carpal tunnel, dorsal to the radial branch of the median nerve. Thumb is to the right. Fingers are to the top. Wrist crease is at the bottom. White arrow points to the lumbrical. Black arrow points to radial branch of the median nerve, whose upper branch supplies the radial half of the index finger and thumb. The arrowhead points to the motor division of the radial nerve branch. Traversing the incision at its upper third is a cutaneous branch to the first web space.

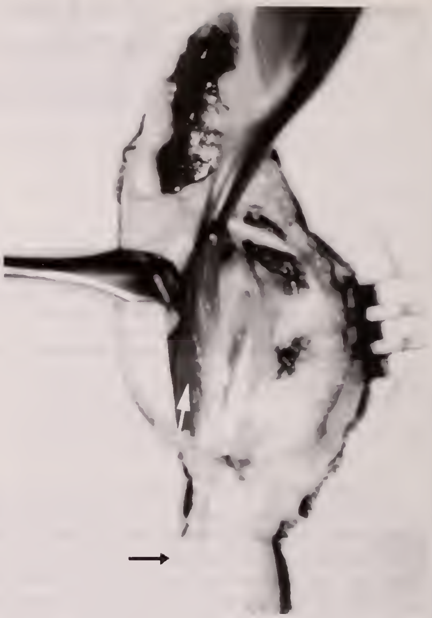

Fig. 2. With the index finger in extension, the forceps exerts distally directed traction to the first lumbrical, pulling its proximal, tendinous origin from the level of the distal forearm to the level of the flexion crease of the wrist. Fingers are to the top. Thumb is to the right. Black arrow indicates proximal level of lumbrical at wrist crease. White arrow points to the lumbrical.

mucopolysaccharidoses; hamartomas of the median nerve; and trauma (1–4). Among its three branches the median nerve has, as its radial-most division, a branch which includes the proper palmar digital nerve to the index finger, as well as the sensory and motor branches to the thumb and thenar muscles. Generally, the origin of the first lumbrical muscle from the profundus tendon of the index finger minimally encroaches on the outlet of the carpal tunnel. Due to its abnormal length in this case, its thickest portion came in contact with the radial branch of the median nerve at the distal edge of the transverse carpal ligament.

The positive Tinel's sign at the distal, radial transverse carpal ligament and the wrist compression sign limited to only the radial 1 1/2 digits distinguish this neuropathological entity. In carpal tunnel syndrome, the first sign would have been negative and the second usually felt in the radial four digits.

The importance of having the patient perform provocative maneuvers and activities during the physical examination is evident. Writing, playing the piano, and holding the bow when playing the cello, activated her anomalous first lumbrical, which lay on the dorsal surface of the radial branch of the median nerve, and compressed it against the distal margin of the transverse carpal ligament on the nerve's volar surface.

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Letter to the Editor

To the Editor: I recently read an article in the March 2004 issue of *The Mount Sinai Journal of Medicine* entitled "If I Were Dean: A Challenge to New Medical Students," by Jeremy Hugh Baron (1). As a student who will begin as a first year medical student at Mount Sinai this August, I thought the article would be especially relevant to me. And it did contain many valuable lessons; however, I found myself respectfully at odds with the section entitled "The Medical Model and the Public."

First, I question Dr. Baron's premise. He divides the field of medicine into two camps. The first is derived from classical Greek texts and called "medical science," or just "medicine." The second, derived from a series of other, unnamed places, is given the title "alternative medicine." The first is based on "genuine science," while the second is "alternative, pre-scientific, non-scientific and pseudo-scientific." The first is valid, the second, by implication, is not. He even goes so far as to assert that "Greek physicians faced the same problem [of the public seeking out unconventional practitioners] 2500 years ago, and in Saxony in 1900 there were 2,029 legally qualified physicians and 1,578 known illegal practitioners," implicitly likening today's practitioners of complementary and alternative medicine (CAM) to illegal practitioners of 1900 Saxony.

While Dr. Baron bemoans the scientific ignorance he finds prevalent among average Americans, I believe that a potentially equally distressing problem could be ignorance, or worse, contempt, among physicians when it comes to CAM. Dr. Baron cites a 1997 survey that reported that 42% of Americans have used some form of alternative medicine, a number that appears to be on the rise. Physicians today practice medicine in a world that demands that CAM be taken seriously. The "problem" of herbal drugs, nutritional supplements and alternative therapies is not going to go away, and in the meantime, physicians need to take responsibility for the health of the population at large. In fact some herbal supplements, far from being useless, are so biologically active that they can lead to harmful outcomes. When the public's safety is at risk, herbal supplements cannot be ignored or made light of.

But the fundamental problem with Dr. Baron's premise is that by setting up two opposing camps of medical models, he ignores the fact that both camps can be used effectively *together* (hence the "C" in "CAM"). By indiscriminately lumping all types of non-Western medicine together into the vague category of "alternative," he makes the gross generalization that "alternative" medicine can never, by very definition, be integrated into the larger category of "medicine." I believe that M. Angell and J.P. Kassirer said it best when they remarked: "There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work. Once a treatment has been tested rigorously, it no longer matters whether it was considered alternative at the outset" (2).

Dr. Baron is right that not all types of "alternative" medicine necessarily fit into his definition of "science." However, if we were to use criteria from one culture or paradigm to judge the validity of another, then Greek-derived biomedicine could just as easily be dismissed based on the fundamental precepts of Chinese medicine. A much more useful guiding model of inquiry, as noted above, would be to separate those methods that are effective from those that have no beneficial effect on the patient, based on outcome, keeping in mind the incredible power of the placebo effect.

Second, I question the tone and attitude used in this section of the address. Dr. Baron describes a woman seeking alternative medicine, who "had a 'rebirthing ceremony' with her husband, in which they shouted and smeared mud and fruit pulp on each other." While the practice may sound strange to us, I do not think that people should be made to seem ridiculous for performing rituals that we do not understand. If physicians are to be effective, it is important that they maintain respect and cultural sensitivity towards all people regardless of their beliefs.

And lastly, even if we do accept Dr. Baron's definition of science as "the conception and construction of refutable hypotheses, their testing by repeatable experiments, followed by publication of the results," some modes of "alternative" medicine can *indeed* be categorized as "scientific." A cursory search on PubMed reveals that herbal medicine is in fact a very hot topic among medical researchers, with exciting work being done right here at Mount Sinai (3). Many traditional herbs have been proven to be effective against pain, illness and disease (4, 5), and this research can be seen as a continuation of the kind of work that has produced digitalis and the vinca alkaloids in the past. For the first time, scientists are beginning to subject the ancient and increasingly widespread practices of yoga, acupuncture, and herbal medicine to the same rigorous standards that they apply to biomedicine (6, 7). While these practices may seem to be outside of the field of medicine, they are becoming more and more mainstream and are gradually gaining acceptance among physicians and scientists grounded in traditional biomedicine.

It is my belief that "medicine," like "science," is also an activity that is "uncertain and is subject to constant revision" (8). I urge my fellow students who have come to Mount Sinai in search of a rigorous education in classical, Greek-based medicine to keep an open mind, and I challenge them, in the spirit of scientific inquiry, to critically examine evidence from *all* sources before drawing conclusions. The future of the field of medicine lies in our hands, and, properly equipped with knowledge of both biomedicine and complementary medicine, we have the power to redefine it.

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CONTENTS

DEAN'S LECTURE

The ER Chaperone BIP Is a Master Regulator of ER Function Linda M. Hendershot 289

GRAND ROUNDS

Measurement of End Points in Heart Failure Trials: Jousting at Windmills? Paul J. Hauptman 298

AAV Vectors for Hemophilia B Gene Therapy Hengjun Chao and Christopher E. Walsh 305

The Institute of Medicine Report "Unequal Treatment": Implications for Academic Health Centers Joseph R. Betancourt and Angela W. Maina 314

Anticoagulation in Pregnant Women with Prosthetic Heart Valves Stephan Danik and Valentin Fuster 322

GENERAL ARTICLES

Acute Myocardial Infarction and Left Subclavian Artery Occlusion in Behçet's Disease: A Case Report Atila Iyisoy, Hurkan Kursaklioglu, Sedat Kose, Zeki Yesilova, Cengiz Ozturk, Kenan Saglam, and Ertan Demirtas 330

Physicians' Religiosity and End-of-Life Care Attitudes and Behaviors Neil S. Wenger and Sara Carmel 335

Fibrous Pleural Tumor with Hypoglycemia: Case Study Naeem Adhami, Raees Ahmed, Patrick A. Lento, Mona Shimshi, Steven D. Herman, and Alvin S. Teirstein 344

Cytomegalovirus Colitis in an Immunocompetent Patient with Amebiasis: Case Report and Review of the Literature Christopher S. Lee, Alexander H. Low, Peter T. Ender, and Henry C. Bodenheimer, Jr. 347

Liver Abscess in Crohn's Disease: A Report of Three Cases David Hazzan, Eric Fishman, Elliot Heller, Mark Chapman, and Joel J. Bauer 351

"Thou Shall Not Kill": Some Legal and Linguistic Problems Jeremy Hugh Baron 355

LETTER TO THE EDITOR

Eighty Hours a Week: A Third-Year Resident's Perspective on Duty-Hour Limitations Shetal I. Shah 358

In Memoriam: Ruth Gail Abramson C3

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Dean's Lecture

The ER Chaperone BiP Is a Master Regulator of ER Function

LINDA M. HENDERSHOT, PH.D.

Abstract

The endoplasmic reticulum (ER) is a command center of the cell that is second only to the nucleus in terms of the breadth of its influence on other organelles and activities. It is a major site of protein synthesis, contains the cellular calcium stores that are an essential component of many signaling pathways, and is the proximal site of a signal transduction cascade that responds to cellular stress conditions and serves to maintain homeostasis of the cell. All eucaryotic cells possess an ER, which can comprise nearly 50% of the membranes of a cell. Its functions can be divided into those that occur on the cytosolic side of the membrane (where protein translation and signal transduction cascades occur) and the luminal space (where most other ER functions take place). Our studies during the past several years have revealed that the ER molecular chaperone BiP is a master regulator of ER function. It is responsible for maintaining the permeability barrier of the ER during protein translocation, directing protein folding and assembly, targeting misfolded proteins for retrograde translocation so they can be degraded by the proteasome, contributing to ER calcium stores, and sensing conditions of stress in this organelle, to activate the mammalian unfolded protein response.

Key Words: ER chaperones, BiP, secretory pathway, ER stress, unfolded protein response.

Glossary of Abbreviations

ADP: adenosine diphosphate
ATF6: activating transcription factor 6
ATP: adenosine triphosphate
ATPase: adenosine triphosphatase
BAP: BiP-associated protein
BiP: binding protein
bZIP: basic leucine zipper
C_H1: first domain of the heavy chain constant region
EDEM: ER-degradation enhancing alpha-mannosidase-like protein
ER: endoplasmic reticulum
ERAD: ER-associated degradation
ER_p72: ER resident protein
Ig: immunoglobulin
LC: light chain
PDI: protein disulfide isomerase
PERK: PKR-like kinase
SERCA: sarco-ER CA2+ ATPase
SRP: signal recognition particle
UPR: unfolded protein response

NEARLY ALL CELL SURFACE and secreted proteins, as well as the resident proteins of all organelles connected with the secretory pathway (endoplasmic reticulum, Golgi, lysosomes, and secretory vesicles), are synthesized on membrane-bound polyribosomes, where they are first translocated across the endoplasmic reticulum (ER) membrane and then folded and assembled in the ER lumen (Fig. 1). The environment that the nascent chain enters would appear to be a very hostile setting for protein folding, and yet even dedicated secretory cells like β islet cells of the pancreas, hepatocytes, and antibody secreting plasma cells, which can produce thousands of proteins/minute, do so with very few catastrophes. Unlike the cytosol, the ER is an oxidizing environment, which promotes disulfide bond formation between cysteine residues, contains large calcium stores, and is crowded with numerous partially folded proteins and subunits. All of these conditions have been shown to dramatically and adversely affect protein folding *in vitro*. It is now clear that the ER contains a large and diverse group of molecular chaperones, which recognize various features on unfolded proteins thereby ensuring that disulfide bonds are not formed between the wrong proteins or between the wrong cysteines within a protein. They also guarantee that exposed hydrophobic regions that will ulti-

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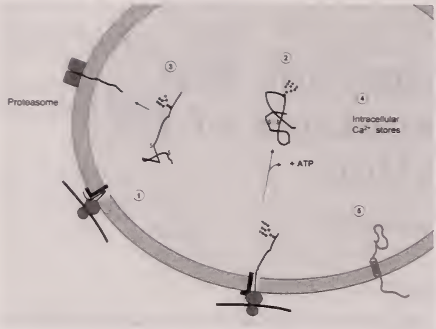

Fig. 1. Functions of the endoplasmic reticulum. (1) The endoplasmic reticulum (ER) is a major site of protein biosynthesis with translation occurring on the cytosolic face of the ER. Nascent proteins are co-translationally translocated across the ER membrane through aqueous channels. (2) Once inside the ER the polypeptide chain is modified by branched N-linked glycans and begins to fold. Folding for many proteins is adenosine triphosphate (ATP)-dependent and the tertiary structure is stabilized by intra- and inter-chain disulfide (S) bonds. (3) If folding fails, the protein must be identified and targeted for retro-translocation back to the cytosol, where it will be degraded by the 26S proteasome. (4) The ER is the storage site for the calcium that will be used in many signal transduction cascades. (5) Finally, if the cell encounters adverse physiological conditions that ultimately affect the environment of the ER, protein folding will be hampered and unfolded proteins will accumulate. A signal transduction response, called the unfolded protein response (UPR), is initiated in the ER, to protect the cell until normal conditions are restored.

mately be buried in the mature, properly folded protein do not lead to aggregate formation in the ER. In addition to their role in aiding and monitoring the maturation of secretory pathway proteins, the chaperones also identify those proteins that fail to mature properly and target them back through the ER membrane for degradation by the cytosolic 26S proteasome in a process that has been referred to as "ER quality control." When adverse physiological conditions arise that prevent proper folding in the ER and thus lead to the accumulation of unfolded proteins in this organelle, a signal transduction cascade is activated which results in the coordinately up-regulation of all ER chaperones, to prevent their aggregation and promote their refolding when normal conditions are restored.

Translocation into the ER

The first step in the synthesis of secretory pathway proteins involves targeting it to the ER membrane, usually via an N-terminal signal peptide. The ER-targeting signal sequence is recognized as it emerges from the ribosome by signal recognition particle (SRP), which halts translation until the ribosome/mRNA, polypeptide chain complex can be attached to the ER membrane via association with SRP and ribosome receptors (1). The nascent chain is then transferred to a proteinaceous channel in the ER membrane called the translocon (2). In a dedicated secretory cell, thousands of ribosomes can be seen attached to the ER membrane, where they begin translocating the N-terminal end of the polypeptide chain, well before translation of the rest of the protein is accomplished. This co-translational translocation would appear to provide many breaches in the permeability barrier that separates the ER lumen from the cytosol and serves to maintain the unique environment of the ER. However, studies reveal that the permeability barrier is carefully preserved during the translocation process. As the nascent chain binds to the ER membranes and begins to be translocated across the ER membrane, the ribosome forms a tight seal with the cytosolic side of the translocon (3). At this time, the luminal side of the translocon is also gated, thus resulting in a translocon that is sealed on both ends. Once the translocating chain reaches a length of ~70 amino acids (~40 inside the ribosome channel and ~30 in the translocon), the luminal end of the translocon is opened (3). To identify the molecule responsible for gating the translocon on the lumen side, ER vesicles were isolated and opened, and luminal contents were removed before the vesicles were resealed. Studies with these vesicles revealed that the translocon was no longer sealed on the luminal side, demonstrating that something released with the luminal contents was responsible (4). By adding back the whole luminal contents or various luminal proteins, it was determined that the ER chaperone binding protein (BiP) was responsible for maintaining the permeability barrier of the translocon during the early stages of protein translocation (4). BiP was released once the nascent chain reached a length of ~70 amino acids, thus opening the channel so that the protein could be translocated into the luminal space. The remaining ribosomal seal on the cytosolic face of the translocon ensures that the environment of the ER is maintained and that nascent proteins move into the ER, as opposed to sliding back to the cytosol.

Protein Folding and Assembly Inside the ER

As the translocating chain enters the ER, well before translation is complete, it is often modified by the addition of N-linked glycans, which serve to direct or limit the pathways along which the protein can fold (5). Folding can begin as soon as a portion of the protein enters the ER, making it very different from *in vitro* folding assays, which only involve full-length proteins. This co-translational folding introduces special constraints and additional problems, since in many cases the N-terminal region of a protein must interact with more C-terminal regions to yield the correctly folded form of the mature protein. In order to inhibit "inappropriate interactions" between the "wrong" regions of a protein during its biosynthesis, a group of resident ER proteins, which have been termed "molecular chaperones" for this very reason, bind and protect the nascent chain until the "correct" region becomes assessable. To date more than 10 chaperones, as well as numerous regulators and co-factors for these chaperones, have been identified in the mammalian ER (6, 7). The Hsp70 family member BiP was the first eukaryotic ER chaperone to be identified, due to its association with the incompletely assembled subunits of antibody molecules (8, 9), a system that continues to be a model for studying BiP's interactions with unfolded proteins. Antibodies are composed of a series of immunoglobulin (Ig) domains that fold independently of each other into a compact structure composed of two twisted β sheets stabilized by a single disulfide bond (10). Although the overall structure of the different domains is extremely similar, the folding requirements and dependence on BiP are very different. BiP binds transiently to some Ig domains (e.g., most C_H domains and some V_L and V_H domains) (11, 12), while other domains appear to fold rapidly and stably without ever interacting with BiP (e.g., C_L) (13). Only the C_H1 domain, which pairs with the C_L domain of the light chain and provides the site for its covalent attachment, interacts stably with BiP in the absence of light chains (LCs) (14). The interaction of this domain with BiP is crucial to controlling Ig assembly and transport, because deletion of this domain, and the resulting ablation of BiP binding, allows the secretion of unassembled and partially assembled Ig intermediates (14).

Two theories were proposed to account for this unique feature of the C_H1 domain. First, in addition to BiP's normal binding to extended, hydrophobic sequences that exist on nascent chains before they fold, BiP might also bind to hydrophobic faces on folded protein subunits before they assembled into multimeric complexes. Alternatively, if BiP only interacted with unfolded linear sequences, then the C_H1 domain might remain unfolded until it paired with LCs. This assembly-dependent folding, first proposed by the Haas lab (15), was somewhat at odds with the belief that ER quality control only allowed properly folded subunits to assemble. By monitoring disulfide bond formation in each heavy chain domain as an indication of folding, we demonstrated that indeed the C_H1 domain is not folded in the absence of light chains, while all the other domains fold and form their intra-domain disulfide bond (16). Interestingly, LCs are not required as a scaffold to induce C_H1 domain folding, but instead act in some undefined way to displace BiP from the heavy chain, thus allowing it to fold (16). Only LCs in which both domains are folded can perform this function. This constraint might be important in controlling the assembly of the pre-B cell antigen receptor, where each LC domain is provided by a separate protein (i.e., V_{preB} and λ_5) (17), as well as in monitoring the variable region of the LC, which can undergo extensive mutation during Ig repertoire development.

BiP (18, 19), like all Hsp70 family members (20), binds and hydrolyzes adenosine triphosphate (ATP), which controls its chaperoning function (20). The ATP-bound state of Hsp70 proteins represents an "open" configuration, which allows them to associate with unfolded substrates. The presence of a DnaJ co-factor in the complex catalyzes the rapid hydrolysis of ATP to adenosine diphosphate (ADP), "locking" the Hsp70 protein onto the unfolded protein. DnaJ proteins exist in all species and organelles: the yeast ER contains three DnaJ proteins (21), while the mammalian ER possesses at least five DnaJ orthologues. The next step in the Hsp70 adenosine triphosphatase (ATPase) cycle is the exchange of ATP back into the nucleotide binding cleft, which "reopens" the Hsp70 protein and releases the unfolded protein. In bacteria and the mitochondria of eukaryotic cells, GrpE proteins regulate the exchange of nucleotide and promote the folding of Hsp70 substrates (22). Although no GrpE homologues have been identified in the yeast or mammalian ER, other nucleotide-releasing factors exist (23, 24). It is believed that the exchange factors and DnaJ proteins continuously turn the Hsp70 ATPase cycle to promote binding and release of Hsp70 proteins, thus allowing the substrate protein to proceed to an increasingly folded state. In support of this idea, we found that BiP ATPase mutants bind to nascent proteins in the ER and protect them from aggregation. However, the mutants could not be released from these proteins, and as a result the substrate protein failed to complete its folding or be secreted (12).

Thus, BiP binds and protects newly synthesized proteins when they are in an unfolded state, but it must release them so that they can fold (Fig. 2).

When studying the folding and assembly of Ig molecules, we found that the C_H1 domain of unassembled heavy chains remained unfolded in the cell, even though it was capable of folding if BiP was released *in vitro* with ATP (16). This was shown to be due to the fact that BiP did not cycle from the heavy chain *in vivo* and suggested that BiP's ATPase cycle was somehow "stalled" when BiP was associated with unassembled heavy chains (25). This led us to look for regulators of BiP's ATPase cycle. Using chemical cross-linkers to stabilize protein:protein interactions, we found that a luminal DnaJ orthologue, ERdj3, was stably associated with unassembled Ig heavy chains (26). As DnaJ proteins stimulate ATP hydrolysis by Hsp70 proteins and help "lock" them onto unfolded substrates, it is possible that its presence in the BiP:heavy chain complex ensures that BiP is not released prematurely. Using a 2-hybrid screen to identify proteins that interacted with the ATPase domain of BiP, we identified BiP-associated protein (BAP), the first mammalian ER nucleotide-releasing factor (24). BAP binds preferentially to BiP when it is in the ADP-bound form and induces ADP release so that ATP can be substituted back. This leads to the release of BiP from heavy chains *in vitro*. It is possible that light chain association with heavy chains is required to either release ERdj3 so that BAP can enter the complex, or that light chains in some way escort BAP to the complex (Fig. 3).

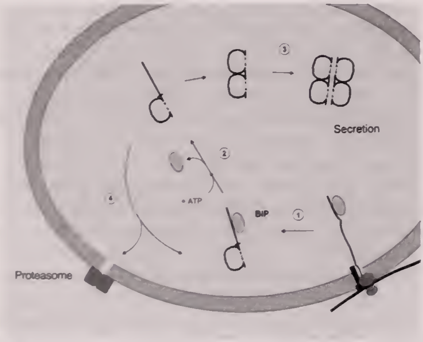

Fig. 2. The molecular chaperone binding protein (BiP) binds to unfolded regions of proteins in the ER. (1) Although proteins can begin to fold co-translationally, some regions of proteins are often slow to fold. BiP binds to these regions and keeps them from aggregating. (2) BiP is released in an ATP-dependent manner allowing the protein to fold completely. (3) If folding occurs properly, the protein will be transported from the ER for eventual cell surface expression or secretion. (4) If it is unable to fold, BiP can either rebind to give the protein another chance or target it for retrotranslocation and degradation.

Disposing of Proteins That Fail to Meet ER Quality Control Standards

Although the vast majority of proteins entering the ER fold quickly and accurately into their proper tertiary structure, protein subunits produced in excess, mutant proteins, and even occasionally normal proteins fail to mature properly. A major function of the ER is to detect these "aberrant" proteins and remove them from the secretory pathway, so they can be disposed of in a process called ER-associated degradation (ERAD) (27). Studies of yeast revealed that the sec61 protein, which is a major component of the translocon, is required for retrotranslocation and degradation of proteins

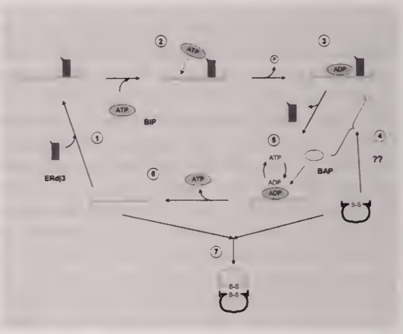

Fig. 3. The ATPase cycle of BiP controls its binding to and release from unfolded proteins and is regulated by co-factors. (1) The co-factor ERdj3 binds to unfolded regions of a nascent Ig heavy chain. (2) It recruits ATP-bound BiP to the substrate. (3) By stimulating BiP's ATPase activity and converting it to the adenosine diphosphate (ADP)-bound form, it "locks" BiP onto the C_H1 domain of the unassembled heavy chain and keeps it in an unfolded protein. (4) In the case of immunoglobulin (Ig) heavy chains, the cycle is stalled here until light chains associate and restart the cycle by an unknown mechanism. (5) The nucleotide-releasing factor, BiP-associated protein (BAP), catalyzes the release of ADP and rebinding of ATP by BiP, shifting it to the "open" conformation. (6) This leads to the release of BiP from the substrate. (7) If the heavy chain is able to combine properly with the light chain, it will assemble into an antibody molecule and be transported to the Golgi for secretion. If not, it can reassemble with ERdj3 for another round or be targeted for degradation.

that fail ER quality control (28). This suggests that the unfolded proteins move back through the translocon or at least through a structure that contains some of the same components as the translocon. How proteins that have ultimately failed to fold are distinguished from those that are in the process of folding is not completely understood. In the case of the calnexin/calreticulin chaperone family, this involves monitoring the N-linked glycans that decorate most secretory proteins and also serve as binding sites for these chaperones. The N-linked glycan is a complex branched oligosaccharide structure that undergoes modification in the ER and processing in the Golgi as the protein bearing it moves through the secretory pathway. A single glucose sugar is continuously added to and removed from the glycan in the ER as long as a portion of the protein is unfolded (29). Calnexin or calreticulin bind to this monoglucosylated glycan on the unfolded protein (30). If however, the mannose residues are trimmed from n9 residues back to 8 before a glucose residue can be re-added, the protein will be recognized by an ER-degradation enhancing alpha-mannosidase-like protein (EDEM) and pulled from the "folding" pathway. EDEM then targets the protein for retrotranslocation and degradation (31). For proteins that utilize BiP during folding, it is much less clear how terminally unfolded proteins are distinguished from proteins that have not yet folded. Studies of yeast demonstrate that BiP is required for the retrotranslocation of a number of ERAD substrates (28). By making a number of chimeras between domains of unfolded proteins with various half-lives, we found that in mammalian cells the BiP binding domain controls the rate of degradation (32), which strongly implies that BiP plays a role in targeting proteins for retrotranslocation in mammalian cells as well. Since BiP also interacts with nascent proteins as they fold, the question immediately arises as to how these two BiP functions are separated. One possibility is that the different DnaJ co-factors provide the specificity of function (Fig. 2). To date, five DnaJ homologues have been identified in the mammalian ER (ERdj1–5). Three of these (ERdj3–5) are induced by ER stress, a condition that leads to the degradation of an increased number of ER proteins, and one of these (ERdj4) is a membrane-anchored protein that is expressed at very low levels in the absence of ER stress, but is potently up-regulated when folding is adversely affected in the ER (33). ERdj3 associates directly with a number of unfolded and partially folded proteins in the ER along with BiP (26). It is possible that proteins could be transferred from ERdj3 to ERdj4 when folding has ultimately failed, redirecting them from a soluble state in the ER lumen to the ER membrane, so they can be retrotranslocated for degradation. However, there are no data available at this point to either support or refute this hypothesis.

Controlling and Maintaining ER Calcium Stores

The ER plays a vital role in controlling both the level and the release of the calcium stores that are used in many signal transduction programs. The concentration of calcium in the ER has been calculated to be between 0.3 and 1.5 mmol^{-1} (34), a concentration that places it several orders of magnitude higher than those found in the cytosol. The high ER levels are controlled by several transmembrane proteins; the ryanodine and the IP_3 receptors release calcium from the ER stores when they are activated by signal transduction cascades, and the sarco-ER CA2+ ATPase (SERCA) pump, which transports calcium back into the ER (35). Drugs like thapsigargin and A23187 lower ER calcium levels by "poisoning" the SERCA pump and releasing calcium stores, respectively. Interestingly, both of these drugs potently activate the unfolded protein response (UPR) (36), demonstrating that secretory pathway proteins require the high ER calcium levels to fold properly. The calcium in the ER exists largely in complexes with both low-affinity calcium-binding proteins (like calnexin, calreticulin and GRP94), which are also molecular chaperones, and with high-affinity calcium-binding proteins (like reticulocalbin and calstorin) (34, 35). Because BiP is a highly abundant ER protein and possesses scattered clusters of acidic amino acids like several of the other ER chaperones that bind calcium, we measured the ability of BiP to contribute to ER calcium stores by overexpressing BiP and other chaperones in Hela cells and measured the effect on ER calcium levels. Our data reveal that BiP and calreticulin both contribute to the ER calcium stores, whereas overexpression of ERp72 did not significantly increase ER calcium levels (37). The increase observed with BiP was directly due to its ability to bind calcium and not to its chaperoning of another ER protein, since both wild-type and ATPase mutants of BiP were able to perform this function. We calculated that under normal physiological conditions, BiP contributes to ~25% of the stores, with a stoichiometry of 1B2 moles of calcium/mole of BiP.

Monitoring and Responding to Conditions That Affect Protein Folding in the ER

The ER and the rest of the secretory pathway possess a unique intracellular environment, one that is similar to the extracellular milieu that many of the proteins being synthesized will ultimately inhabit. In addition to being influenced by this oxidizing environment that promotes intra- and inter-chain disulfide bonds in secretory pathway proteins, the vast majority of proteins synthesized in this organelle are also modified by N-linked glycans. These conditions and modifications regulate the stability and folding of the nascent polypeptide. Changes in physiological conditions that affect the storage of calcium, the oxidative state or the pH of the ER lumen, or conditions that alter the availability of N-linked glycans can very dramatically and adversely alter protein maturation and lead to the accumulation of unfolded proteins in this organelle. The cell responds to this accumulation by activating a signal transduction pathway, termed the "unfolded protein response" (UPR). The response consists of coordinately up-regulating the transcription of all ER chaperones (36) to protect unfolded proteins and prevent them from aggregating, and also transiently inhibiting protein synthesis (38) to limit the accumulation of unfolded proteins. The inhibition of protein synthesis also induces cell cycle arrest (39), so that cells encountering stress conditions are not propagated. Finally, apoptotic pathways are activated if the stress conditions are not alleviated (40) in order to protect the organism.

The signal for inducing the UPR was understood long before the proteins that transmit the signal were identified. In 1988, Kozutsumi et al. reported that by transiently overexpressing a single unfolded protein they were able to induce the UPR in mammalian cells (41). Follow-up studies by other groups revealed that only a subset of unfolded proteins activated the response; proteins that bound to BiP did (42), whereas proteins that associated with one of the other chaperones like calnexin did not (43). A role for BiP in signaling ER stress was further supported by data showing that the overexpression of BiP, but not of other ER chaperones like protein disulfide isomerase (PDI) or GRP94, was sufficient to block activation of the UPR during ER stress conditions (44). Together these data suggested that the cell somehow determined the amount of BiP that was available or free to monitor the presence of conditions in the ER. If sufficient amounts of BiP were available, conditions must have been good, whereas if BiP became limited, conditions must have been taxing the chaperones present, and therefore the UPR would be activated to coordinatedly up-regulate all ER chaperones. The molecular basis for this level of control awaited the identification of the signaling molecules.

Activation of the mammalian UPR is achieved by three ER-localized transmembrane proteins that "sense" stress through their luminal domains and transduce the stress signal via their cytosolic domains. The Ire1 kinases (α is ubiquitously expressed and β is limited to gut epithelium) (45, 46) are homologues of the single ER stress transducer in yeast, Ire1p (47, 48). Activation of mammalian Ire1 during ER stress stimulates a unique endonuclease activity in its C-terminal region, an activity that is conserved with yeast Ire1p (49). The XBP-1 mRNA, which encodes a basic leucine zipper transcription factor, is the single known target of the mammalian Ire1 endonuclease. Activated Ire1 excises a 26-nucleotide segment from the XBP-1 transcript, which is then relegated to encode a larger remodeled transcription factor, sXBP-1, with an altered transactivation domain tethered to the original DNA binding domain (50, 51). The second signal transducer of the UPR is the double-stranded RNA-activated protein kinase (PKR)-like kinase (PERK), which phosphorylates eIF-2α in response to ER stress (52, 53). This modification serves to transiently block most protein translation, thereby diminishing the accumulation of unfolded proteins in the ER when conditions are not favorable for folding. The third component of the signaling apparatus, ATF6, is a transmembrane protein with a luminal domain and a cytosolic domain that encodes another basic leucine zipper (bZIP) transcription factor (54). In response to ER stress, ATF6 is transported to the Golgi, where it is cleaved by the S1P and S2P proteases, resulting in the release of its cytosolic domain, which then traffics to the nucleus and up-regulates transcription of ER chaperones and folding enzymes, to prevent the aggregation of unfolded proteins and aid in their subsequent folding if stress conditions are resolved (55).

With the identification of the upstream signaling molecules of the UPR and the production of reagents to isolate them, it was possible to determine the molecular basis for sensing stress in the ER. We found that in unstressed cells PERK and Ire1 form a stable complex with BiP (Fig. 4). Agents that alter normal protein folding in the ER promote the reversible dissociation of BiP from the luminal domains of these kinases, which leads to their oligomerization and activation (56). In situations where BiP is overexpressed, the higher levels of BiP allow it to remain bound to the kinases even under stress conditions and therefore to inhibit their activation. The abatement of ER stress results in BiP rebinding to the kinases, attenuating the response (56). Other studies reveal that Ire1p is similarly regulated by BiP in yeast (57, 58). When ATF6 was examined, we found that, like the ER kinases, BiP formed complexes with the luminal domain of this membrane-anchored transcription factor under normal physiological conditions. Induction of ER stress led to a rapid release of BiP from the luminal domain of ATF6, which resulted in its transport to the Golgi where it could be acted on by the S1P and S2P proteases that reside there, thus liberating the cytosolic-oriented transcription factor domain (59). This required an ATP-dependent release of BiP from the luminal domain of ATF6, as BiP ATPase mutants blocked transport and cleavage of ATF6 (59). Together these findings are consistent with BiP serving to inhibit signaling through PERK, Ire1, and ATF6 in the absence of unfolded proteins. Protein misfolding relieves this inhibitory signal and triggers the response either indirectly, by competing for BiP, or directly, by altering the conformation of the signal transducers themselves (Fig. 4). The ATP-dependent release of BiP from the transducers suggests that they may possess unfolded regions in the absence of stress, which serve as conventional BiP binding sites. Thus, stress conditions in the ER appear to be sensed by monitoring the availability of a single molecular chaperone, BiP. When it becomes limiting and the transducers are activated, a signal transduction cascade is put in motion that results in the up-regulation of all ER chaperones and many of their regulators. This ensures that the appropriate chaperone will be available regardless of the requirements of the individual protein, without having to monitor levels of all the chaperones.

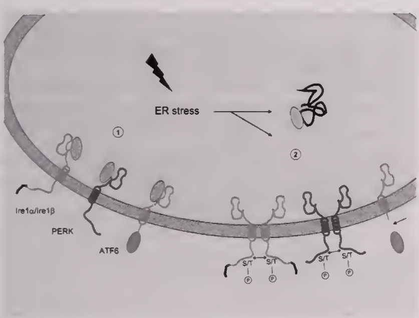

Fig. 4. Sensing stress conditions in the ER. (1) Researchers have identified three resident ER transmembrane proteins that serve as signal transducers for ER stress. They include Ire1α/β, PKR-like kinase (PERK), and activating transcription factor 6 (ATF6). During normal physiological conditions their luminal domains are bound to BiP, which keeps them in an inactive state. (2) When unfolded proteins accumulate in the ER due to stress conditions, BiP is released from the luminal domains to interact with the unfolded proteins. This results in the dimerization or oligomerization of Ire1 and PERK, which leads to their activation and downstream signaling. The release of BiP from ATF6 allows it to traffic to the Golgi, where the cytosolic transcription factor domain is liberated from the membranes, so that it can drive transcription of UPR target genes.

P=phosphate, S/T=serine or threonine residue.

Summary

The ER houses protein complexes that allow it to carry out its diverse multitude of functions, which include protein translocation, protein folding, the identifying and degrading of proteins that fail to mature properly, the storing of calcium, and finally sensing and responding to abnormal physiological conditions that adversely affect protein biosynthesis in this organelle. A single ER chaperone, BiP, plays a critical role in controlling or contributing to each of these functions (Fig. 5). With the exception of calcium storage, BiP's ATPase activity is required for it to perform all of these different roles, suggesting that BiP may recognize the specific proteins involved as though they were unfolded proteins, and further, that its binding and release will be regulated by DnaJ and nucleotide-releasing factors (as has been demonstrated for its role in protein folding). Five mammalian ER DnaJ orthologues have been identified; it is possible that each is specific for a different function and that they provide an additional layer of specificity to BiP.

Acknowledgments

I gratefully acknowledge the colleagues in my laboratory, whose work provided much of the data presented in this article. In particular I wish

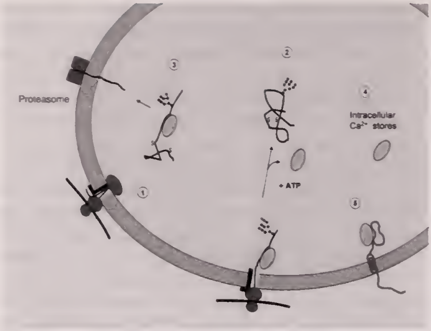

Fig. 5. BiP is integrally involved in all major ER functions. (1) BiP binds to the translocon and seals the luminal end until the ribosome is seated on the cytosolic side and the elongating polypeptide is ~70 amino acids long. (2) BiP binds to unfolded regions of nascent proteins and directs their folding and assembly in an ATP-dependent manner. (3) BiP recognizes improperly folded proteins and targets them for degradation. (4) BiP is a calcium-binding protein and contributes to the ER calcium stores. (5) BiP binds to the luminal domains of the ER stress transducers and keeps them in an inactive state. When levels of free BiP become limiting, BiP is released and the transducers are activated.

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Measurement of End Points in Heart Failure Trials:

Jousting at Windmills?

Paul J. Hauptman, M.D.

Abstract

Advances in the treatment of congestive heart failure, a condition of increasing incidence and prevalence, have been made possible by knowledge gained from randomized clinical trials. The selection of end points in these trials has become a pivotal step in the drug and device approval process. In part because of the success of earlier trials, the number of study subjects required in order to realize an important improvement in survival has increased. This has led to the development of alternative combined and composite end points, often including surrogates for mortality. The limitations of these end points, the specific challenges associated with studies of patients with decompensated and diastolic heart failure, and other issues encountered during and after completion of heart failure trials, are discussed.

Key Words: Heart failure, end points, clinical trials.

> "Fortune disposes our affairs better than we ourselves could have desired: look yonder, friend Sancho Panza, where thou mayest discover somewhat more than thirty monstrous giants, whom I intend to encounter and slay, and with their spoils we will begin to enrich ourselves...."
>
> Don Quixote, in *The Adventures of Don Quixote,* Chapter VIII (1)

Congestive heart failure (HF) is a condition of increasing incidence and prevalence, with a pronounced impact on patients, providers and payers (2–5). According to statistics from the American Heart Association, there are 550,000 new cases in the United States each year, and males and females aged 40 who do not have a diagnosis of HF have a one-in-five lifetime chance of developing the disease (2). Epidemiologic data from Framingham and Olmstead County, and from other evaluations suggest that HF is a condition characterized by considerable morbidity and mortality (6–8). The situation places enormous pressure on physicians to devise strategies that can decrease mortality and improve quality of life for patients with the disease.

For over twenty years, advances in therapeutic options for HF have been driven by knowledge gained from numerous phase II and phase III clinical trials, many with acronyms that say little about the drug or device under study but nonetheless reflect optimism about the process and/or ultimate outcome of the drug discovery and development effort (PRECISE, BEST, MERIT, PROVED, SOLVD and IMPRESS, to name a few (9–14). Randomized, placebo-controlled double-blinded clinical trials (RCTs) are more than just experimental studies: they are pivotal for therapy approval and labeling; help to confirm and generate hypotheses about and/or provide insight into disease pathophysiology; and facilitate a therapy's acceptance into clinical practice now heavily influenced by evidence-based decision-making. The selection of appropriate end points for these trials is therefore a crucial component of clinical trial design, and by extension, drug and device approval.

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Standard End Points

Traditionally, the standard so-called "hard" end point in trials that measure drug or device efficacy has been all-cause mortality. Cardiovascular mortality, all-cause hospitalization and heart failure hospitalization are often used as secondary stand-alone end points. Although clearly a binary outcome (the study subject is either dead or alive), mortality can be subject to uncertainty. Evaluation of the mode of death can be limited by lack of detail, in large part because many deaths occur out of hospital. Formal, unbiased adjudication processes reduce the degree of ambiguity, but categorization of mode of death is best viewed as an artificial construct. First proposed by Hinkle and Thaler (15), the classic description of mode of death as sudden arrhythmic versus circulatory failure has been criticized (16–18) because of significant overlap and difficulties in recreating the events leading up to death. Some investigators have proposed a variety of alternative classification schemes (19–21) to assist in clarifying mode of death. This has relevance, because a drug or intervention that simply causes a redistribution among the various terminal events will not be considered a significant advance.

Combined and Composite End Points: Is There a Role for a Substitute for Mortality?

With multiple randomized clinical trials demonstrating mortality benefits, mostly additive, from the use of angiotensin-converting enzyme inhibitors (of between 20–25%), beta-adrenergic antagonists (of at least 30–35%, depending on the drug) and the aldosterone antagonist aldactone (31%) (22–24), the proverbial bar for achieving statistical significance has been raised. The power calculations in clinical trials now must reflect the fact that appropriately treated patients are living longer with heart failure. In lieu of designing trials that require 5000 or more patients to show a survival benefit, alternative combined or composite end points have been proposed (Table). One commonly used end point is the combination of all-cause mortality and heart failure hospitalization, since it joins together death from any cause with a disease-specific event. Alternatively, the combination of death, hospitalization, and either emergency department visit or unscheduled office visit has been combined to form an "event" end point.

Packer has proposed a composite of heart failure hospitalization plus change in quality of life score plus change in end-diastolic dimension (25). One of the challenges with this and other composites that incorporate multiple possible outcomes is that it is difficult if not impossible to devise a scoring system that, on a sound scientific basis, weighs the relative importance of the different parameters. This can be best highlighted in the A-HeFT trial, in which points are assigned according to the outcome achieved (26). For example, a significant change in quality of life as measured by the Minnesota Living with Heart Failure Questionnaire at six months will be assigned 2 points, whereas death will be 3 points (27).

TABLE
Types of End Points

Combined	All-cause mortality and heart failure hospitalizations
Composite	Composite heart failure hospitalization plus change in quality-of-life score plus change in left-ventricular end-diastolic dimension
Surrogate	Neurohormonal panel Ejection fraction Hemodynamics

The use of composite end points, increasingly common in phase II and as secondary end points in phase III trials, has encouraged an ongoing debate about the role of surrogate, nonmortality end points (28, 29). A fundamental requirement for a surrogate end point is that the relationship between the surrogate and mortality is established; that is, there is a strong correlation, preferably with an underlying pathophysiologic basis, between the two measures of drug efficacy. Further, the patient cannot have direct knowledge of the surrogate itself; hence echocardiographic parameters qualify as surrogates whereas distance on a six-mile corridor walk test and quality of life scores do not.

Recent results have suggested that the use of nonmortality endpoints including surrogates is fraught with risk. We learned more than a decade ago that suppression of premature ventricular contractions by anti-arrhythmic drugs (30), once thought of as a useful surrogate, could be associated with higher mortality (31). In the heart failure area, a multitude of drugs that provided favorable changes in hemodynamics during short-term administration were associated with higher mortality with chronic use (32–35). Data from the U.S. carvedilol studies demonstrated that exercise distance does not correlate with survival benefit (9). These misconceptions should occur less frequently with increasing knowledge about the factors underlying the evolution of left ventricular remodeling and the mechanism of action of the drug under study. However, the favorable impact of a drug on one part of disease progression or expression does not automatically translate into a benefit for the patient, and therein one finds a challenge for clinical trialists.

Nevertheless, despite potential drawbacks, several surrogates offer promise, especially measurements of left ventricular size (36, 37) and neurohormonal levels. For example, changes in ventricular dimensions and volumes or ejection fraction (measured by echocardiography, magnetic resonance imaging or nuclear imaging) have been associated with outcomes and may provide a true window on long-term prognosis (36). Indeed, the remarkable array of factors in univariate and multivariable analyses associated with outcomes in heart failure suggests that the list of potential surrogates is much larger.

One particularly problematic end point is health-related quality of life (HRQoL), an important consideration in any chronic cardiovascular disease (38, 39). Several studies have demonstrated the problems associated with measurement of HRQoL in heart failure trials, including the participation of a select minority of subjects to whom HRQoL instruments are administered (40, 41). In many studies, the number of participating patients is not detailed and the frequency of measurements is limited. Furthermore, the instrument selected is pivotal, especially since changes in total or domain scores within each instrument may not be highly correlated with changes in another instrument (42). Indeed, the performance of quality-of-life measurements relative to a functional test (exercise time) has been disappointing (43).

Various so-called "fast tracks" to quality of life have been proposed, specifically patient global clinical assessment ratings and specific symptom ratings (such as dyspnea) on simplified 3-point, 5-point or visual analog scales (14, 44). However, the simplicity of these measures also represents a drawback. For example, while health perception on a visual analog scale was associated with New York Heart Association Class in one trial, there was significant overlap on the individual patient level (14). The predictive value for downstream adverse clinical events was reasonable, but the timing and frequency of such measurements remain uncertain. Further, as Rector asked: "Are simple symptom assessments adequate measures of therapeutic efficacy? One doesn't know what is actually being measured when patients say they feel better" (45).

Similarly difficult has been the interpretation of acute hemodynamic responses to drug therapy. Important placebo effects can be demonstrated (46). More important, reliance on acute changes in hemodynamics and cardiac output, previously the basis for dose selection in a series of phase III trials, failed to translate into a survival benefit for active drug treatment. Therefore, a lowering of pulmonary capillary wedge pressure can no longer be viewed as a replacement for survival.

Other potential end points attempt to address clinical events that mark a worsening clinical status and include: rates of discontinuation of study medication due to worsening heart failure; need for intravenous inotropic therapy; need for intravenous diuretic therapy; and days alive outside hospital.

End Point Determination in Decompensated Heart Failure

The high event rate for patients with decompensated or New York Heart Association Class IV symptoms suggests that this should be a simpler population to study than cohorts consisting of patients with lesser severity of disease, at least in terms of the number of subjects required to reach specific clinical end points. However, recruitment can be more difficult, and a placebo-controlled trial is subject to frequent investigator-driven crossover into active therapy. The need for rescue therapy has been considered part of a composite end point that suggests worsening of the clinical status of the patient and by extension, prognosis. In all likelihood, the decision to use additional or alternative therapies is a legitimate measure of patient deterioration or at the very least the physician assessment of such deterioration and, as an end point, represents a step forward in gauging efficacy relative to the simple dyspnea scale that was previously in use (47).

End Point Determination in Diastolic Heart Failure

Given a low rate of death due to isolated diastolic heart failure relative to advanced systolic heart failure, a trial that demonstrates a survival advantage must be appropriately powered. The recently published CHARM protocol demonstrates this point (48). Therefore, the use of surrogate and other end points is once again an issue, but the selection of candidates appears to be more limited. Exercise distance, performance on a cardiopulmonary exercise test or quality of life may be appropriate, but the correlations between these parameters and mortality in diastolic failure are not well established.

End Point Determination in Device or Surgical Therapy

Trials of devices and operative approaches to the treatment of heart failure have been performed but present unique methodological problems. The definition of a placebo group is difficult at best, since sham surgery is generally not permissible and blinding can be challenging (49). Comparison of outcomes relative to historical controls is usually an unsatisfactory option. There are often technical issues during the evaluation process of a new technology; these can affect power calculations and exacerbate center-specific effects. Furthermore, the costs related to the performance of device and surgical trials are also significantly higher than for drug studies, at least on a per subject basis.

End Points for the Future

With an appreciation for the various factors that influence or characterize remodeling comes an opportunity to consider the use of surrogate candidates that represent changes in molecular, cellular, morphologic or functional expression. These include the evaluation of individual cardiomyocyte size or function (50, 51) and measurement of beta-receptor subtype (52). However, availability of endomyocardial biopsy specimens with which to perform many of these assays will almost certainly be limited. Another possible candidate is a composite neurohormonal panel consisting of factors such as brain natriuretic peptide, norepinephrine, endothelin and angiotensin II. However, as with any of the composite end points, the selection and relative importance of the different neurohormones (and the magnitude of change in levels) are not known. Furthermore, any new end point should meet the same standard as that of end points in general: each must be valid, reliable and responsive to change.

Other Issues in End Point Measurement

Heterogeneity of Outcomes and Subgroup Analysis

Large multi-center trials, by definition, have the advantage of a significant number of study subjects and sites. As a result, there is also the potential for an array of heterogeneous outcomes, which can be analyzed by baseline factors such as patient age, gender or race; study site; region or country; dose of drug; etiology of heart failure; and other factors. Examples have included the comparison of African Americans vs. Caucasians (10, 53, 54), Europe vs. the United States (55), dosing regimens (56) and etiology (57). Although beyond the scope of this paper, the legitimacy of subgroup analysis can be called into question as the number of subgroups analyzed increases, especially if it is performed on the basis of *post-hoc* identification of efficacy trends between groups that were not defined at the start of the trial. A difference detected between subgroups in a surrogate outcome is particularly burdened with potential misinterpretations.

Long-Term Trends

Given the possible length of the approval and dissemination process for new treatments for heart failure, the results of any given trial, especially those that require an extended follow-up period, are at risk of appearing to be obsolete. New therapies are always seen in the context of standard therapy at the time of approval, not the time of randomization. The importance and influence of long-term trends has been demonstrated in both the device and drug fields (58, 59) and is, in effect, a risk that may not be avoidable.

Efficacy of Related Drugs

Chemical, pharmacokinetic, pharmacodynamic and clinical trial data suggest that drugs within "a class" are not all alike (60). Nevertheless, once efficacy is determined for a particular drug, the replication of the findings with a different drug within the same class is of dubious scientific merit unless the comparator group is the proven drug, not a placebo. An argument has been made that differences in background therapy can justify the performance of a placebo-controlled trial (59), and there may be some reasonableness behind the argument. Unfortunately, pivotal, so-called "head-to-head" clinical trials are rarely performed (61). Rather, trials are generally designed to define a new niche for the drug under development, or not designed at all, in which case a "carry over" effect from a different indication can occur based on pricing and other strategies. For example, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers approved for treatment of hypertension have been used in heart failure, even in the absence of supporting data.

After the Trial

Approval vs. Use

As noted, despite restrictive language in labeling, once a drug is approved, physicians may find avenues for use outside the original intent. A useful demonstration of this phenomenon in the heart failure field involves milrinone, approved for "the short-term intravenous treatment of acute CHF. There is no experience in controlled trials with infusions for periods exceeding 48 hours" (62). Nevertheless, much of the use of the drug is outside the 48-hour window, despite the fact that the official position of the American College of Cardiology/American Heart Association classifies chronic continuous infusions as a class IIb indication and intermittent infusions as a class III indication (63).

Efficacy vs. Effectiveness

The overall effectiveness of a drug shown to be efficacious within the confines of a clinical trial is often difficult to measure. As Heiat et al. have demonstrated, there has been, in general, an under-representation of women, minority groups and the elderly in heart failure trials (64). Whether a drug can be shown to be effective in all groups of patients, indeed whether an RCT can predict clinical outcomes, is often not established. This idea is well represented by Messerli et al., who stated: "Trials examine primarily medical interventions; randomization permits comparisons of interventions not confounded by the individuality of patients. Here is the paradox of the trial: it is the best way to assess whether an intervention works but is arguably the worst way to evaluate who will benefit from it…" (65). The problem may also be exacerbated by polypharmacy, both in terms of drug-drug interactions and cost.

Conclusion

We find ourselves in an era of "evidence-based medicine," and our practice in heart failure is dictated in large part by the outcomes of randomized clinical trials, which have supplanted pathophysiology as the primary driver of the selection of therapeutic options. Despite the challenges brought about by our own successes in the treatment of heart failure, useful clinical trials can still be performed. Recognition of the importance of end point selection, study population and doses is crucial. Careful interpretation of the data is also important, as is a willingness to accept the limitations of the data. Unlike Don Quixote, who saw everything in the context of his own preconceptions, we need to recognize that the p value is not a windmill to be vanquished.

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Grand Rounds

AAV Vectors for Hemophilia B Gene Therapy

Hengjun Chao, M.D., and Christopher E. Walsh, M.D.

Abstract

Adeno-associated viral (AAV) vector is attracting significant interest for use in gene therapy for genetic diseases, because of its unique and advantageous characteristics, compared to other currently available viral vectors. Eight natural serotypes of AAV have been identified, of which AAV serotype 2 is the one best characterized and most widely used in current gene delivery studies. The application of AAV serotype 2 in hemophilia B gene therapy is a promising development in gene therapy for genetic diseases such as hemophilia. Preliminary studies have demonstrated relation and distinction of host, genome sequences, replication, tropism, packaging of recombinant virions and cross-reactivity of neutralizing antibodies among different serotypes of AAV. This review summarizes the progress of studies in AAV serotypes and pertinent applications in hemophilia B gene therapy. The latest progress in gene delivery of coagulant factor IX (for hemophilia B) using AAV serotype vectors is described in detail.

Key Words: Hemophilia B, gene therapy, adeno-associated virus, serotype.

Hemophilia B Gene Therapy

Hemophilia B is a sex-linked hemorrhagic disease resulting from deficiency in coagulant factor IX (FIX) (1). It occurs in one of 30,000 live male births in all populations (1, 2). The main clinical manifestation of the disease is unpredictable, recurrent, spontaneous bleeding in soft tissues and/or major joints. Recurrent bleeding in large joints usually leads to crippling arthropathies in a majority of severely affected patients (3, 4). The clinical severity of hemophilia B corresponds to the level of circulating FIX. Severe hemophilia occurs in less than 1% of FIX activity. With moderate hemophilia, 1–5% of FIX activity, there is infrequent, spontaneous bleeding. The presence of at least 5% of FIX seems to protect those with mild hemophilia against spontaneous bleeding (1, 4). Currently, the standard treatment for hemophilia B is infusion of FIX concentrates in response to a bleeding event (4). Prophylactic infusions of factor concentrates in children significantly reduce the frequency of bleeding episodes and subsequent joint disease, thus improving the quality of life of these patients (5). However, the high cost of purified factor products makes lifelong prophylactic infusion impractical. Administration of recombinant factors would enable the patients to be free of the potential pathogenic contamination associated with plasma-derived FIX concentrates (6). However, many patients in undeveloped countries, and even in developed countries, lack adequate medical insurance coverage; they are still at risk for infection from contaminant viral pathogens while receiving plasma-derived FIX concentrates (1, 3, 4). In addition, prevailing responsive replacement treatment cannot prevent the occurrence of progressive joint damage, which is a result of recurrent bleeding episodes occurring in those patients with the most severe cases (3, 4). Somatic gene therapy could provide sustained expression of functional FIX safely and conveniently via the introduction of the correct FIX gene into patients, circumventing the above-mentioned problems in hemophilia B treatments.

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Hemophilia B has been one of several targets in an effort to achieve the first definitive gene correction of a genetic disease (7). Factors contributing to this effort include: the relatively small size of the FIX coding sequence (~1.5 kb), which makes it easy to be packaged and delivered by most available vectors; the relatively long half-life of the FIX protein (~20 hours); the fact that no precise regulation or specific tissue/organ is required for functional FIX expression; the well-established *in vitro* and *in vivo* assays necessary to evaluate FIX antigen and activity; the well-characterized hemophilia B animal models (FIX knock-out mouse (8) and naturally occurring hemophilia B canine (9)); and most important, the fact that only a slight increase of the circulating FIX level (5% of physiological level) results in significant clinical benefit for patients (4).

Generally, the FIX gene can be delivered via either non-viral or viral mediation. Currently, viral vectors are being generated mainly from murine Moloney leukemia retrovirus, herpes simplex virus, adenovirus, adeno-associated virus (AAV) and lentivirus. They are being used as a gene therapy modality in hemophilia B and other genetic diseases (7). In recent years, dramatic progress has been made using viral vectors in gene therapy for hemophilia B (10–22). *Ex vivo* transduction of fibroblasts with murine Moloney retroviral vectors has expressed high levels of FIX *in vitro* but has failed to produce the similar FIX yield *in vivo*, for several reasons (7). Although a clinical trial has shown that subcutaneous injections of *ex-vivo* transduced fibroblasts with murine Moloney retrovirus-based vectors have expressed functional FIX and reduced hemorrhagic frequency in two hemophilia B children (19), reproducible outcomes from more patients are needed to verify the efficacy of this procedure. One group has also demonstrated long-term expression and partial hemophilia phenotype correction in the Chapel Hill strain of hemophilia B canines, following intraportal injections of retroviral vectors and partial hepatectomy (14). Low transduction efficiency to post-mitotic cells and aggressive procedures (partial hepatectomy) required to promote cell cycling restrict the practical application of retroviral vectors (7). Recombinant adenoviral vectors express transient high levels of functional FIX, but the severe vector-related immune response and toxicity significantly limit the application of adenovirus vectors (23), especially in patients with chronic genetic diseases such as hemophilia. The advent of gutless adenoviral vectors, with the dramatic reduction of immune response and toxicity associated with adenoviral elements, may extend the application of adenoviral vectors in hemophilia gene therapy (24). The novel lentiviral vector has demonstrated promising preliminary results in hemophilia B gene therapy (25, 26). However, compared to other vectors, the relatively low FIX yield associated with the potential incapability of infecting quiescent cells vector-related toxicity remain optimized before this vector system comes to practical application in human patients (25–27). Compared to retrovirus, adenovirus and lentivirus, which are the only nonpathogenic viral vectors, recombinant adeno-associated virus (rAAV) is considered one of the best vectors for FIX gene transfer. This is based on its unique and advantageous characteristics including vector-related toxicity and safety, target tissue/organ tropism, and persistence of transgene expression (22, 28–30).

Gene Therapy for Hemophilia B Using AAV Serotype 2 Vectors

In the past decade, AAV has attracted significant interest as a promising gene delivery vector, due to its unique characteristics (22, 28–30). AAV is a group of nonpathogenic, replication-defective small DNA viruses. Out of the six natural serotypes of AAV, AAV serotype 2 (AAV2) is the best characterized and most widely used (30). Current understanding of AAV biology, the expertise in manipulating recombinant AAV, and the production and purification of rAAV have resulted from studies on AAV2 (30). A majority of applications of AAV as gene transfer vectors were also performed on the basis of AAV2 (28–30).

AAV2 is a small (~20 nm of diameter) DNA virus containing 4675 bp of linear, single-stranded genome. The nonstructure rep genes are located within the left part of the genome and encode four proteins, designated Rep78, Rep68, Rep52 and Rep40. The structure cap genes encode the three capsid proteins—VP1, VP2 and VP3—of which protein VP3 is the most abundant and accounts for 90% of the total virion capsid. The only cis components required to generate AAV2 vectors are the two 145 nucleotide-inverted terminal repeats (30). These terminal repeats are required for the replication and packaging of the recombinant genome into newly formed AAV virions (30). Advances in the production and purification of rAAV type 2 vectors, including the elimination of helper virus (ad) contamination (31), and purification by column chromatography (32), have helped in the advancement of AAV2 use in gene therapy applications. Like nonpathogenic wild type AAV type 2 (wtAAV2), rAAV infects both dividing and nondividing cells and establishes latency for the life of the cell. Although the natural route of infection for wtAAV is upper respiratory, rAAV has demonstrated efficient infection and long-term expression of transgenes in the brain, liver, muscle, retina, and vasculature of experimental animals (30).

Hemophilia B gene therapy using rAAV2 has made great progress in recent years (33, 34). Intraportal vein injection of rAAV2 has expressed sustained therapeutic levels of FIX in hemophilia B mouse and dog models, and partially corrected the abnormal hemostasis parameters of the animals (18, 21, 35, 36). With a canine FIX (cFIX) expression cassette carrying a liver-specific promoter, a group reported expression of supra-physiological levels of functional cFIX (up to 20 μg/mL) and complete hemophilia phenotype correction in hemophilia B mice following intraportal delivery of the rAAV2/FIX vectors (20). This vector was optimized by adding a post-transcriptional element (37) and administered to the liver of the Chapel Hill strain of hemophilia B dogs. A subsequent report from the same group demonstrated that this optimized cFIX expression cassette expressed therapeutic levels of FIX (~240 ng/mL, ~5% of physiological level) and achieved the complete correction of the abnormal whole blood clotting time (WBCT) in one of the two dogs (21). Both dogs received the high dose of rAAV2 vectors (2.8×10^{12} and 4.6×10^{12} rAAV2 particles/kg). This was the first report to demonstrate expression of therapeutic levels of FIX (5% of physiologic level) from AAV2 vectors in large animal models, though only one dog showed this therapeutic level of FIX and complete correction of WBCT, and a dramatic reduction in the frequency of spontaneous bleeding, after receiving a high dose of rAAV2 vectors (21). Another group recently reported expression of therapeutic levels of FIX in hemophilia B dogs after hepatic delivery of rAAV2 vectors carrying a strong liver promoter (36). However, due to frequent exposure to blood products, a high prevalence of hepatitis virus infections and subsequent liver diseases was observed in the hemophilia population (1, 3, 4), which may restrict the application of AAV targeting liver for gene therapy in these patients. In fact, a patient enrolled in a recent phase I clinical trial using hepatic delivery of AAV2 vector for hemophilia B gene therapy attained therapeutic levels but transient expression of FIX. The peak-and-through plasma levels of FIX coincided with an increase and decrease of the patient's serum transaminase (38). The real cause(s) responsible for diminished FIX expression was unclear and may be complicated. However, the potential contribution from cryptic liver damage could not be completely excluded.

Skeletal muscle is a good targeting tissue for somatic gene therapy (39, 40). The large bulk of this muscle allows for multiple injections of a large volume of the viral vectors. Direct intramuscular injection is in general well-established medical practice and is applicable to vector delivery. Skeletal muscle has shown the capability of secreting a range of functional proteins, especially those capable of secreting FIX and carrying out post-translational modification of FIX (γ-carboxylation) (41–45). The pilot study demonstrated that direct intramuscular injections of rAAV2 vectors are capable of facilitating long-term (over 1.5 years) transgene (LacZ) expression without detectable cellular immune response against AAV vector and the transgene (46). An rAAV2 vector carrying human FIX canine DNA (cDNA) was then produced and administrated via direct intramuscular injections to the Chapel Hill strain hemophilia B dogs. Formation of anti-human FIX inhibitory antibodies disturbed assays on circulating FIX antigen and activity in the dogs, even though evidence demonstrated expression of rAAV-derived human FIX in the injected skeletal muscle in the dogs (17). To bypass interference of anti-human FIX inhibitor, two rAAV2 vectors expressing cFIX were constructed and high-titer rAAV2 vectors ($\sim10^{13}$) were produced (10). After direct intramuscular injection of rAAV2/cFIX into two Chapel Hill strain hemophilia B canines, expression of about 1% of normal level of canine FIX was detected by enzyme-linked immunosorbent assay (ELISA) assay (10). The activity of the cFIX resulted in reduction of WBCT from more than 60 minutes before injections, down to less than 20 minutes after AAV2 injections in two canines. The cFIX level and reduction of WBCT persisted for three years in one dog and for nine months in the second dog, at which time it was sacrificed (10). The cFIX expressed was not sufficient to completely correct the bleeding phenotype of the dogs. Both canines still suffered from spontaneous bleeding, which required intermittent infusion of normal dog plasma (10). Our results were consistent with a report using a similar strategy in the same strain of hemophilia B canines. In that study, where as much as 1×10^{13} rAAV2/cFIX virion particles per kilogram of the canine body weight was administered, up to 1.2% of normal level of cFIX was expressed into the circulation of the Chapel Hill strain hemophilia B dogs (13). The dogs showed reduction of WBCT from over 60 minutes before AAV injection, down to 15 – 20 minutes after injections, while still suffering from spontaneous bleeding (13). Further investigation determined that formation and persistence of neutralizing antibodies (NAB) against AAV2 in both dogs was detected after virus injection (10). The NAB significantly inhibited rAAV2 vectors from transducing target cells *in vitro* (10).

Investigation of biodistribution of rAAV2 vectors after intramuscular injections revealed that a majority of the AAV2 vectors were trapped around the injection site, which acts as the resource to express functional FIX. Heparan sulfate proteoglycan (HSP) acts as receptor for AAV2 (47). It was also found that AAV2 tropism is limited to slow-twitch muscle fibers rather than fast-twitch fibers, associated with an overexpression of HSP on slow muscle fibers (48). The limited tropism of AAV2 to certain myofibers may partially account for the relatively low FIX yield from injected skeletal muscle.

These studies demonstrate the promising outlook for rAAV2 as a safe and effective approach for hemophilia B gene therapy. Compared to the aggressive intraportal injection, and taking into account the high prevalence of hepatic viral infections in adult hemophilia patients, the safe and convenient intramuscular injection of AAV has its own advantages in hemophilia B gene therapy. However, FIX levels in hemophilia B canines were subtherapeutic (less than 2% of normal level, failing to completely correct hemophilia phenotype) despite high doses of rAAV2 (up to 1×10^{13} AAV particles per kilogram of animal body weight) (10, 13). When scaling up from a 10 kg dog to a 70 kg adult patient, it is difficult to produce enough rAAV2 vectors for expressing minimal therapeutic FIX levels in patients, based on current AAV production protocol (31). In fact, a gene therapy clinical trial based on intramuscular delivery of rAAV2 exhibited undetectable FIX in the circulation of the recipients despite FIX expression detected at the injection site (15). Alternate strategies to re-administer AAV2 vectors may be impeded due to the formation and persistence of high titer of NAB against AAV2 in the animal after primary injections of AAV2, which probably makes re-administration of rAAV2 ineffective (10, 49 – 52). In addition, high prevalence of NAB against AAV2 in the general human population (53 – 55) may also restrict application of rAAV2 in human gene therapy. Due to the frequent exposure to blood products, and thus more susceptibility to viral infection (3, 4, 56), the hemophilia population may have a higher prevalence of AAV2 NAB than does the general population. Strategies are required to bypass AAV NAB and/or increase rAAV transduction efficiency in target tissue to reach a therapeutic level of FIX.

AAV Serotypes as Gene Transfer Vectors

Eight natural serotypes of AAV have been cloned and sequenced (30, 49, 57 – 59). They were termed serotypes 1 – 8 in accordance with their unique serological (immunological) characteristics, and the sequences of isolation and characterization (60 – 65). AAV serotype 1 was first isolated from the rhesus monkey, based on seroepidemiological evidence, but frequently infects human population; however, it has not yet been isolated from the human species (49, 53, 60, 62, 64, 65). AAV serotype 2, 3 and 5 are human viruses and each demonstrates a high prevalence of infection in the general human population, based on seroepidemiological investigation results (53, 60, 62, 63, 65, 66). AAV serotype 4 is of African green monkey origin and rarely infects humans, based on seroepidemiological studies, although it can infect human cells *in vitro* (58, 61, 62). Serotypes 1 and 6 share >99% amino acid homology in their capsid proteins, and sequence analysis supports a recombination event between serotypes 1 and 2, resulting in the genesis of AAV6 (49).

Comparison of the serotype capsid amino acid sequences suggests that heterogeneity exists among AAV serotype capsids (49, 57 – 59, 67), a finding consistent with serological study results (53, 62, 63, 65, 66). Preliminary studies on AAV serotypes as gene transfer vectors also suggest different tropism and transduction efficiency on different cell types (when compared to AAV2 or with each other) (11, 49, 51, 57, 68 – 70). Xiao and colleagues reported that AAV1 demonstrated higher transduction efficiency and transgene expression than AAV2 in skeletal muscle in C57BL/6 mice, while using α anti-trypsin as the reporter gene; however, it is the reverse when targeting the liver of the mice (49). Although AAV3 shows high homology with AAV2 in genome sequence, a study demonstrated capacity of AAV3-based vector to infect erythroid hematopoietic cells in which AAV2-based vector failed (70), indicating that differential tropism exists between the two genetically close vectors. In addition, AAV3 vector was reported to be capable of evading anti-AAV2 NAB and successfully infecting rabbit airway epithelial cells (51, 52) despite high homology and cross-reactivity between AAV2 and AAV3. However, AAV6, which is more constant from AAV2 than from AAV3, demonstrated a higher efficiency in evading pre-existing AAV2 NAB and infecting the airway epithelial cells (51, 52). It was also reported that AAV serotypes 4 and 5 have different host cell tropisms in the brain when compared to each other and to AAV2 (69). A vector based on AAV serotype 5 but not on serotype 2 demonstrated the capacity to infect the apical surface of airway epithelium and facilitate gene transfer (68). AAV serotype 6-derived vectors showed 15–74-fold higher transduction efficiency than AAV2 vectors in airway epithelia (71). A very recent report shows superhepatic transduction of the newly identified AAV serotype 7 and 8 vectors in rodents (72). In summary, the above reports demonstrated higher tropism of AAV serotypes vectors, with the exception of AAV2, indicating the feasibility of increasing AAV-mediated gene transfer efficiency in different cell types by using non-AAV-serotype-2 vectors. They also show the feasibility of evading pre-existing anti-AAV2 NAB by using other AAV serotype vectors.

We tested the transduction efficiency of rAAV serotype 1–5 vectors in the skeletal muscle of the mouse. Our results demonstrated super-intramuscular transduction efficiency of rAAV1 and rAAV5 over rAAV2 vectors (11). A subsequent investigation of rAAV serotype vectors targeting rat retina and mouse liver found that rAAV1 vector was superior for efficient transduction of liver, followed in order by rAAV serotypes 5, 3, 2, and 4 (73, 74), which is in accord with that in skeletal muscle (11, 75, 76). Surprisingly, this order changed when the vector was introduced into rat retina. Types 5 and 4 were most efficient, followed by type 1 (73).

AAV-Serotype-Mediated Gene Therapy for Hemophilia B

Direct intramuscular injection of AAV2 vector has proven to be a safe and convenient procedure to provide sustained expression of the transgene (FIX, etc.) in gene therapy for hemophilia B and other genetic diseases (34). However, only subtherapeutic expression of FIX was seen in large animal models and human patients after intramuscular injection of even high doses of AAV2 vectors, which is attributed to the limited muscular transduction efficiency of AAV2. In our attempt to pursue more efficient intramuscular transduction of AAV vectors and higher FIX expression, we found higher skeletal muscle transduction efficiency using serotypes of AAV vectors, especially AAV1 vector, than of AAV2 (11, 77).

We then tested the five serotype AAV/cFIX vectors for FIX expression in skeletal muscle. A dose of 2.5×10^{11} vector genomes of AAV/cFIX serotypes 1, 2, 3, 4 and 5 was injected into the hind limbs of nonobese diabetic/severe combined immune deficient (NOD/SCID) mice (n=5, for each experimental group). Plasma was tested at monthly intervals for cFIX using an established ELISA assay specific for cFIX. We detected cFIX in all experimental animals. No cFIX antigen was detected in plasma samples taken from control animals receiving equivalent doses of serotyped AAV/GFP. As expected and consistent with the green fluorescent protein (GFP) studies, cFIX antigen levels in mice receiving AAV types 1, 3, 4 and 5 were higher than those in the AAV2/cFIX mice. The amount of cFIX in the plasma of mice receiving types 1, 3 and 5 was unexpected. Levels higher than 100 μg/mL and 10 μg/mL of cFIX were detected in the mice receiving AAV types 1 and 5, respectively. This represents a 10^3 and 10^2 increase of cFIX, respectively, when compared to mice receiving AAV2/cFIX. Western blot results verified the ELISA data showing that supraphysiological levels of cFIX were expressed in the plasma of AAV1/cFIX-injected mice. We determined the AAV1/cFIX protein to have a molecular weight of approximately 64 Kd. FIX levels detected in the AAV2-injected mice in our studies were lower than those in a previous report using AAV2 to express human FIX (hFIX) in muscle of Rag1 knock-out mice (~100 ng/mL vs. 300 ng/mL) (78). Differences in the transgene (cFIX vs. hFIX), transgene cassette (including different polyA signal sequence and position of intron), AAV production and titration, and mouse strains (NOD/SCID vs. Rag1) between the two studies may be responsible for the different FIX expression outcomes.

To extend the results observed in SCID mice, we tested AAV1 and AAV2 serotype vectors for FIX expression and hemophilia B phenotype correction in FIX knock-out mice (77). These mice develop spontaneous bleeding consistent with the hemophilic phenotype and have no detectable FIX mRNA, due to deletion of the 5′ untranslated region through exon 3 of the mouse FIX gene (8). In addition to spontaneous bleeding, these animals show prolonged *in vitro* clotting activity (APTT) and cannot survive tail-clip-induced trauma, due to sustained bleeding (8). A dose of 1×10^{11} AAV1/cFIX vector genomes was injected into the hind limbs of FIX knock-out mice (n=10).

Compared to AAV1/GFP controls, high levels of cFIX antigen were measured only in plasma of rAAV1/cFIX injected animals. Peak antigen expression was observed 3–5 weeks post-injection, consistent with all previous studies using AAV2 vectors. Western blot quantitation verified the presence of ~64 Kd protein at levels approximately 2–5 times that of normal plasma. Accordingly, the abnormal APTT of the mice was completely corrected in the AAV1/cFIX-treated animals and all the AAV1/cFIX treated mice survived the tail clip challenge.

In comparison, cohorts of FIX knock-out mice injected with 1×10^{11} AAV2/hFIX vector genomes generated anti-FIX antibody which was detected as early as one week after AAV injection. When we gave cyclophosphamide (CTX) to the AAV2-injected mice, a peak cFIX level of 100 ng/mL (2% of normal) was measured. APTT results in these animals were consistently elevated above the normal range, but were not manifested by normal clotting activity. The differences between serotype specific transduction were further distinguished by tail clip challenge resulting in survival of all AAV1-treated mice compared to 50% of AAV2-treated mice.

Based on our studies, AAV type 1 vectors appeared to be most efficient in muscle and liver transduction, followed by types 5, 3, 4, and finally 2 (11). A previous report comparing AAV1 and AAV2 vectors in muscle using different reporter genes in mouse strain also described increased vector transduction for type 1, albeit at lower levels (49). However, a very recent report verified our observation of rAAV1 transduction superiority in muscle while delivering FIX gene (79).

Discussion

The accumulated evidence suggests that current protocols of gene therapy for hemophilia B using rAAV2 targeting skeletal muscle are unable to provide the therapeutic levels of FIX necessary to prevent spontaneous hemorrhages in large animal models and/or human patients (10, 13, 15), although they seemed promising for small rodent models (78). Our preliminary studies demonstrate that rAAV1 vectors may bring about a dramatic increase in FIX expression after transducing skeletal muscle in large animal models, thus leading to successful gene therapy for hemophilia B; however, it remains to be proven. Our preliminary results in the hemophilia B mice show complete phenotype correction of hemophilia after intramuscular injection of rAAV1 vectors. To our knowledge, this is the first time hemophilia phenotype correction has been achieved by intramuscular injection of AAV vector. However, we realized, from our own experience (10) and the literature (12, 18, 20, 21), that there is a lower FIX yield in canine models than in rodent models, when both receive the same dose of AAV vectors. While our preliminary studies demonstrate that rAAV1 led to particularly robust transduction in mouse skeletal muscle, it is conceivable that human skeletal muscle may not demonstrate the same improved tropism. However, experience with rAAV2 infection across many mammalian species suggests that this is unlikely (10, 12, 17, 80–82).

Our preliminary studies also demonstrated that a simple change of the rAAV/cFIX capsid without modifying the cFIX expression cassette would dramatically increase the cFIX yield (11). rAAV tropism difference, based on the unique capsid structure, may account for promotion of cFIX expression. Optimization of the FIX expression cassette by the use of stronger (tissue-specific) enhancers/promoters (83), and post-transcriptional elements will be performed to increase FIX expression (21, 37).

Because the AAV serotype capsid is the only difference among our serotype AAV/cFIX vectors, it is reasonable to hypothesize that virus binding and entry into the target cells (47, 84, 85), intracellular trafficking (86, 87), and nuclear transportation, all of which are associated with the unique capsid of the AAV serotypes, may be the major machinery accounting for significant differential transgene (cFIX) expression efficiency of AAV serotype vectors. This seems true in the case of AAV serotypes targeting skeletal muscle for cFIX expression (11), and hence should be universal in all gene transfer. However, in some cases, the robust transgene expression from non-AAV-serotype 2 may be impeded due to the silence of the promoter in certain cells and/or the limited capacity of certain cells to process the transgene (like post-translational modification), even though the cells were efficiently infected or the transgene mRNA was transcribed abundantly. We need further testing of targeting more than skeletal muscle and delivering more than canine FIX gene in more than mouse animal models.

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Grand Rounds

The Institute of Medicine Report "Unequal Treatment":

Implications for Academic Health Centers

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Abstract

Background: The United States has achieved dramatic improvements in overall health and life expectancy, largely due to initiatives in public health, health promotion and disease prevention. Academic health centers have played a major role in this effort, given their mission of engaging in research, educating health professionals, providing primary and specialty medical services, and caring for the poor and uninsured. However, national data indicate that minority Americans have poorer health outcomes (compared to whites) from preventable and treatable conditions such as cardiovascular disease, diabetes, asthma, cancer and HIV/AIDS. Two factors contribute heavily to these racial and ethnic disparities in health: minorities are subjected to adverse social determinants, and they are disproportionately represented among the uninsured. In the last twenty years, however, the literature has highlighted the fact that racial and ethnic disparities occur not only in health, but also in health care.

The Institute of Medicine Report, "Unequal Treatment." The Institute of Medicine (IOM) was asked to determine the extent of racial and ethnic disparities in health care. Their report, entitled "Unequal Treatment," found that racial and ethnic disparities in health care do exist, and that many sources, including health care systems, health care providers, patients and utilization managers, are contributors.

Recommendations from "Unequal Treatment": Implications for Academic Health Centers. The IOM Report, "Unequal Treatment," provides a series of recommendations to address racial and ethnic disparities in health care, targeted to a broad audience (the executive summary and full IOM Report can be found at www.nap.edu under the search heading "Unequal Treatment"). Several of the recommendations speak directly to the mission and roles of academic health centers, and have clear and direct implications for patient care, education, and research.

These recommendations include collecting and reporting health care access and utilization data by patient's race/ethnicity, encouraging the use of evidence-based guidelines and quality improvement, supporting the use of language interpretation services in the clinical setting, increasing awareness of racial/ethnic disparities in health care, increasing the proportion of underrepresented minorities in the health care workforce, integrating cross-cultural education into the training of all health care professionals, and conducting further research to identify sources of disparities and promising interventions.

Conclusion: "Unequal Treatment" provides the first detailed, systematic examination of racial/ethnic disparities in health care, and provides a blueprint for how to address them. The report's recommendations are broad in scope, yet have direct implications for academic health centers.

Key Words: Institute of Medicine Report, unequal treatment, racial disparities, ethnic disparities, health care, racial minorities, ethnic minorities, minority health, academic health centers.

Background

Over the past two hundred years, the United States has achieved dramatic improvements in overall health and life expectancy, largely due to initiatives in public health, health promotion and disease prevention. Academic health centers have played a major role in this effort, given their mission of engaging in research, educating health professionals, providing primary and specialty medical services, and caring for the poor and uninsured (1). Nevertheless, despite interventions that have improved the overall health of the majority of Americans, racial and ethnic minorities have benefitted significantly less than others from these advances. National data indicate that minority Americans

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have poorer health outcomes (compared to whites) from preventable and treatable conditions such as cardiovascular disease, diabetes, asthma, cancer, and HIV/AIDS (2).

Multiple factors contribute to these "racial and ethnic disparities in health." First and foremost, research has demonstrated that social determinants such as lower levels of education, lower socioeconomic status, inadequate and unsafe housing, racism and living in close proximity to environmental hazards disproportionately impact minority populations and thus contribute to their poorer health outcomes (3–7). One unfortunate example of the impact of social determinants is the fact that three of the five largest landfills in the country are in African-American and Latino communities, thus contributing to some of the highest rates of pediatric asthma among these populations (8). Second, lack of access to care also takes a significant toll, as uninsured individuals are less likely to have a regular source of care and are more likely to report that they delay seeking care or that they have not received needed care—all resulting in experiencing avoidable hospitalizations, emergency hospital care and adverse health outcomes (9–11). Also, minorities are more likely to be uninsured than their white counterparts, with data from the US Census Bureau demonstrating that in 2002, 32% of Hispanics and 20% of African-Americans were uninsured, compared to only 11% of whites (12).

In the last twenty years, however, the literature has highlighted the fact that racial and ethnic disparities occur not only in health, but also in health care. In fact, these disparities in quality of care for those with access to the health care system contribute to the larger issue of racial and ethnic disparities in health. Research in this area has shown that minorities receive a lower quality of care when they are in the health care system, even when controlling for social determinants and insurance status. For instance, disparities have been shown to exist in the utilization of cardiac diagnostic and therapeutic procedures (African-Americans are referred less often than whites for cardiac catheterization and bypass grafting) (13–17); prescription of analgesia for pain control (African-Americans and Latinos receive less pain medication than whites for long bone fractures and cancer) (18–20); and surgical treatment of lung cancer (African-Americans receive less curative surgery than whites for non-small-cell lung cancer) (21). Disparities have also been seen in referral for renal transplantation (African-Americans with end-stage renal disease are referred less often than whites to the transplant list) (22); treatment of pneumonia and congestive heart failure (African-Americans receive less optimal care than whites when they are hospitalized for these conditions) (23); and the utilization of general services covered by Medicare (i.e., immunizations and mammograms) (24). Again, perhaps the most important issue that should be noted about all of these studies is that disparities occurred even when variations in such factors as insurance status, income, age, co-morbid conditions and symptom expression are taken into account. Racial/ethnic disparities in health are unacceptable, yet understandable, given the persistent racial and socioeconomic inequalities in the US today (which include minorities, on the whole, having lower levels of education and lower annual incomes than whites) (25). Research highlighting racial/ethnic disparities in health care sheds light on a heretofore less visible crisis that has until recently been given little national attention.

As a result of this work, in 1999 the United States Congress commissioned the Institute of Medicine (IOM) to further study the issue of racial/ethnic disparities in the health care system. The IOM, part of the National Academy of Sciences and chartered by Congress to advise the federal government on issues of health policy, medical care, research, and education, was asked to:

- Assess the extent of racial/ethnic differences in health care that are not otherwise attributable to known factors such as access to care (e.g., ability to pay or insurance coverage);

- Evaluate potential sources of racial and ethnic disparities in health care, including the role of bias, discrimination, and stereotyping at the individual (provider and patient), institutional and health systems levels; and

- Provide recommendations regarding interventions to eliminate health care disparities.

The Institute of Medicine Report, "Unequal Treatment"

To study this issue, the IOM convened a committee of academicians, medical educators, health service researchers, health policy makers, economists, social psychologists, social scientists, lawyers, practicing physicians and nurses—some with experience and knowledge in the area of disparities, and others with expertise and proven leadership in other aspects of health care delivery and research. This approach is consistent with the goal of the IOM to assemble an objective and open-minded group of committee members who can effectively evaluate the evidence and come up with findings and recommendations. Given that the charge of the committee was limited to disparities in health care (versus the larger issue of health outcomes) once access had been achieved, specific areas of exploration included: health system factors (financial and institutional arrangements, structural processes of care, etc.); provider factors (communication in the medical encounter, the effect of race/ethnicity on clinical decision-making, etc.); and consumer factors (patient preferences). To carry out its responsibilities over the 18 months of the study, the committee reviewed a significant amount of evidence from five main sources, including a review of the literature (with strict inclusion and exclusion criteria), commissioned papers (on topics ranging from an exploration of health care disparities to the economic, ethical and legal ramifications of disparities in health care), expert testimony, focus groups of patients and providers, and a public workshop. The final report, entitled "Unequal Treatment: Confronting Racial/Ethnic Disparities in Healthcare" (26) was released on March 20, 2002. The major findings were as follows:

- Racial and ethnic disparities in health care exist and, because they are associated with worse health outcomes, are unacceptable.

- Racial and ethnic disparities in health care occur in the context of broader historic and contemporary social and economic inequality, and there is evidence of persistent racial and ethnic discrimination in many sectors of American life.

- Many sources—including health systems, health care providers, patients, and utilization managers—may contribute to racial and ethnic disparities in health care.

- Bias, stereotyping, prejudice, and clinical uncertainty on the part of health care providers may contribute to racial and ethnic disparities in health care.

- A small number of studies suggest that certain patients may be more likely to refuse treatments, yet these refusal rates are generally small and do not fully explain health care disparities.

Recommendations from "Unequal Treatment": Implications for Academic Health Centers

The IOM Report "Unequal Treatment" provides a series of recommendations to address racial and ethnic disparities in health care, targeted to a broad audience (the executive summary and full IOM Report can be found at www.nap.edu (27) under the search heading "Unequal Treatment"). Several of the recommendations speak directly to the mission and roles of academic health centers, and have clear and direct implications for patient care, education, and research.

Improving Systems to Address Disparities: Recommendations for Patient Care

Collect and report health care access and utilization data by patient's race/ethnicity. One of the foremost challenges in the effort to eliminate racial/ethnic disparities in health care is to detect these differences when they are present. Many of the findings in "Unequal Treatment" were based on national studies or regional studies that utilized data that was readily available (e.g., hospital discharge data), but they were not designed to capture health care disparities based on race and ethnicity. As a result, the report cannot give a local "snapshot" of the issues facing a particular health care system or hospital. This limitation is compounded by the fact that race and ethnicity data collection systems, when present (such as in Medicare databases), have only recently begun to collect data on patient groups outside the standard categories of "white," "black," and "other" (28). Consequently, not only do we lack the appropriate systems to track and monitor racial and ethnic disparities in health care, but we also know little about the disparities that other minority groups (Hispanics, Asian-Americans, Pacific Islanders, Native Americans and Alaska Natives) may be experiencing. In sum, standardized data on racial and ethnic disparities in care are generally unavailable. Federal, private, and state-supported data collection efforts are scattered and unsystematic, and most health care systems, hospitals, and health plans (with a few notable exceptions) do not collect data on patients' or enrollees' race, ethnicity, or primary language.

It is clear that our ability to track and eliminate racial and ethnic disparities centers on our ability to collect race and ethnicity data in a systematic and standardized fashion. This highlights the pivotal role academic health care centers could play in the systematic collection of the necessary data. This would enable us to effectively identify disparities locally, and then implement strategies to monitor and eliminate them as part of quality improvement and performance measurement efforts. This leads us directly into our next recommendation.

Encourage the use of evidence-based guidelines and quality improvement. "Unequal Treatment" highlights the subjectivity of clinical decision making as a potential cause of racial and ethnic disparities in health care. Specifically, this occurs when clinicians offer different diagnostic and treatment options to different patients (consciously and unconsciously) based on their race or ethnicity, even in the presence of well-delineated practice guidelines. To remedy the problem, the authors recommend the widespread adoption and implementation of evidence-based guidelines. For instance, there now exist evidence-based guidelines for the management of diabetes, HIV/AIDS, cancer screening and management, and asthma—all areas where significant disparities exist. As part of ongoing quality improvement efforts in academic health centers, particular attention should be paid to implementing of evidence-based guidelines for all patients, regardless of their race and ethnicity, and monitoring progress accordingly. The goal of evidence-based guidelines is to ensure that all patients get the highest quality of care, regardless of race, ethnicity, culture or class. Academic health centers can play a major role in achieving this.

Support the use of language interpretation services in the clinical setting. The lack of interpreter services in health care systems can lead to patient dissatisfaction, poor comprehension and compliance, and ineffective/lower quality care for patients with limited English proficiency (29–37). Doctor-patient communication without an interpreter, in the setting of even a minimal language barrier, is recognized as a major challenge to effective health care delivery (29–31). Research in this area has shown that Spanish-speaking patients discharged from the emergency room are less likely than their English-speaking counterparts to understand their diagnosis, prescribed medications, special instructions, and plans for follow-up care (32); less likely to be satisfied with their care or willing to return if they have a problem; more likely to report problems with their care (33); and less satisfied with the patient-provider relationship (33). In addition, Hispanic patients whose physicians don't speak Spanish are more likely to omit medication, miss office appointments, and visit the emergency room for care (36). The report's recommendation to support the use of interpretation services has clear implications for health care delivery in academic health centers.

Addressing Disparities through Training: Recommendations for Education

Increase awareness of racial/ethnic disparities in health care. Recent surveys have shown that neither physicians nor patients are aware of the extent, or the severity, of racial and ethnic disparities in health care in the US. For example, a national mail survey of 2,608 physicians (whose primary activity is patient care) conducted by the Kaiser Family Foundation in 2001 found that a majority of those surveyed (mainly white) said that the health care system "never" (14%) or "rarely" (55%) treats people unfairly based on race/ethnicity (38). In contrast, a similar phone survey of 3,884 members of the public, conducted by the Kaiser Family Foundation in 2000 found that 36% of Hispanics and 35% of African-Americans (compared to 15% of whites) felt that they were treated unfairly in the health care system based on their race or ethnicity. Perhaps even more revealing, 65% of African-Americans and 58% of Hispanics (compared to 22% of whites) were afraid of being treated unfairly in the future, based on their race/ethnicity. Increasing awareness of racial and ethnic treatment disparities among health care professionals is an important first step in addressing disparities in health care. Academic health centers can increase awareness and education regarding health disparities through several venues, including grand rounds, public relations campaigns and newsletters, and as part of educational curricula (38).

Increase the proportion of underrepresented minorities in the health care workforce. Recent data available from the American Medical Association indicate that of the 70.5% of US physicians whose race and ethnicity is known, Hispanics make up 3.5%, African-Americans 2.6%, and American Indian and Alaska natives less than 0.5%. Minority physicians are also poorly represented in specialties such as cardiology, surgery, and radiation oncology (40). Data regarding the racial/ethnic composition of medical school faculty is no different, with minorities comprising only 4.2% nationally. Moreover, approximately 20% of this latter group are located at three historically black medical schools (Howard University School of Medicine, Meharry Medical College, and Morehouse School of Medicine), and three Puerto Rican medical schools (Universidad Central del Caribe School of Medicine, Ponce School of Medicine, and the University of Puerto Rico School of Medicine) (41). The situation with regard to the future health care workforce is only slightly brighter. Despite comprising 30% of the population, minority students accounted for approximately 10% of medical school graduates in 2001. A majority of these students were African American (65%), with smaller percentages of Mexican American students (22.6%), mainland Puerto Ricans (6.4%) and Native Americans (5.9%) (42). Among medical school graduates in 2001, nearly half of minority graduates indicated plans to practice in underserved areas, compared to less than one-fifth of non-minority students. In sum, given the important role academic health centers play in training our future health care workforce, it is increasingly important that recruitment, retention and promotion of minorities at all levels of the academic ladder become an integral part of human resources policy. The goal of this recommendation is to develop a diverse health care workforce that can meet the needs of an increasingly diverse population, not only from the standpoint of direct clinical care, but also from the standpoint of leadership, health system design, and research.

Integrate cross-cultural education into the training of all health care professionals. There is a growing literature that delineates the impact of sociocultural factors, race, and ethnicity on health and clinical care (43). Health care professionals aren't shielded from diversity, as patients present varied perspectives, values, beliefs and behaviors regarding health and well-being. These sociocultural differences between patient and provider influence communication and clinical decision making, and are especially significant, given the evidence that links provider-patient communication to patient satisfaction, regimen adherence, and subsequently, health outcomes (44, 45). Thus, when sociocultural differences between patient and provider aren't appreciated, explored, understood or communicated effectively in the medical encounter, patient dissatisfaction, poor adherence, poorer health outcomes and racial/ethnic disparities in care may result (46). Cross-cultural education is a strategy to address these issues directly. The goal of cross-cultural education is to improve providers' ability to understand, communicate with, and care for patients from diverse backgrounds. Training in this area focuses on enhancing awareness of sociocultural influences on health beliefs and behaviors, and providing skills to understand and manage these factors in the medical encounter.

Given the findings of "Unequal Treatment" and the description of how stereotyping by health care providers might lead to disparate treatment based on a patient's race or ethnicity, it is now felt that that cross-cultural curricula should be expanded to explore the roles of race, ethnicity, and culture in clinical decision-making. For instance, over the course of their medical education, doctors are taught the "prescriptive theory of clinical decision-making." Simply put, this theory states that clinical decisions should rely on the detailed exploration of two variables: the presentation of symptoms and the probability of disease (through the application of Bayes' theorem) (47). Simultaneously, doctors are taught a set of heuristics or "clinical gestalts" with the premise that there are certain "hallmark" symptoms for conditions. These heuristics then become shortcuts for clinical decision-making (for example, cough and fever probably equals bronchitis or pneumonia). Although this runs counter to what we are taught about generating a detailed review of symptoms and a broad differential diagnosis, as we practice under greater stress and time pressure we become more susceptible to using these "shortcuts" in our clinical decision-making.

Doctors are also taught that their own personal background, and the characteristics of the patient and the clinical setting, should be excluded from consideration in the formulation of clinical decisions. Social cognitive theory, however, has brought to our attention the ways in which natural tendencies to stereotype might influence clinical decision-making. Every day we are faced with enormous amounts of information that we must sift through in order to make decisions. As a result, we all share the subconscious strategy of attempting to simplify our decision-making process and lessen our cognitive effort by using "categories" or "stereotypes" in which we apply beliefs and expectations about groups of people to individuals from that group (48–50). Interestingly, we may not be aware of our attitudes or consciously endorse stereotyping. Nevertheless, when individuals are mentally assigned to a particular class or group, the characteristics assigned to that group are subconsciously and automatically applied to the individuals. It should be emphasized that this is a normal, functional, adaptive cognitive process that is oftentimes automatic, and most likely centered on (in rank order) race, gender, and age—characteristics that manifest visually (49). Most important, we tend to activate stereotypes most when we are stressed, multitasking and under time pressure—the hallmarks of the clinical encounter.

For example, many medical students and residents are often trained—and minorities cared for—in academic health centers or public hospitals located in socioeconomically disadvantaged areas. As a result, doctors may begin to equate certain races and ethnicities with specific health beliefs and behaviors (e.g., "these patients" engage in risky behaviors or "those patients" tend to be noncompliant) that are associated more with the social environment (poverty, etc.) than their patients' racial/ethnic backgrounds or cultural traditions. This "conditioning" phenomenon may also occur if doctors are faced with certain racial/ethnic patient groups who tend to avoid the more aggressive forms of diagnostic or therapeutic interventions. The result over time may be that doctors begin to believe that "these patients" don't like invasive procedures, and thus the doctors may not offer them as options very ardently, if at all. In the case of African-Americans, for example, this opinion could become a self-fulfilling prophecy. Based on historical factors of segregation and medical experimentation, African-Americans have been more mistrustful of the health care system than any other racial or ethnic group (with Latinos not far behind) (46). This mistrust may contribute to wariness in accepting or following recommendations, undergoing invasive procedures, or participating in clinical research. This in turn may lead doctors to believe that African-Americans are less adherent or less interested in aggressive treatments. Again, this stereotyping is a natural and expected—but no less dangerous—phenomenon that may affect the way doctors make decisions and offer specific interventions to various patients based on their race or ethnicity.

In summary, cross-cultural curricula should provide an overview of health care disparities, a framework for understanding and improving the clinical decision-making process (including strategies to avoid stereotyping), and skills for effectively communicating and negotiating across cultures. These curricula could be incorporated into the training for all health care professional.

Identifying Strategies to Eliminate Disparities: Recommendations for Research

Conduct further research to identify sources of disparities and promising interventions. While the literature that formed the basis of the findings and recommendations of "Unequal Treatment" provided significant evidence for racial and ethnic disparities, additional research is needed in several areas. First, most of the disparity literature focuses on differences between African-Americans and whites; much less is known about the experiences of other minority groups. This may be due to the way data has been collected, and the fact that information on health access and utilization may not be as readily available for other subgroups (Hispanics, Asian-Americans, Native Americans, etc.). Improving our ability to collect racial and ethnic patient data should facilitate this process, but in instances where those systems are not yet in place, racial and ethnic patient data may be collected prospectively in the setting of clinical or health services research. Second, until now much of the literature on disparities has focused on defining areas where they exist, but much less has been done to identify the multiple factors that contribute to disparities, and very little has been done to test specific interventions to address them. Future health disparities research should focus on these steps, and academic health centers can be at the cutting edge of this agenda.

Conclusion

The Institute of Medicine Report "Unequal Treatment" provides the first detailed, systematic examination of racial/ethnic disparities in health care, and provides a blueprint for how to address them. The report's recommendations are broad in scope, yet have direct implications for academic health centers, given their mission of engaging in research, educating health professionals, providing primary and specialty medical services, and caring for the poor and uninsured. The strategies presented here will improve the care of all patients, not just those who are members of racial and ethnic minorities. As such, the IOM's recommendations should inform the quality improvement, education and research agendas of academic health centers in the future, and thus help to bridge the "quality gap." Eliminating disparities should no longer be considered a marginal or "add-on" issue, but instead a critical part of the mission of academic health centers. Ultimately, academic health centers can ill afford to have patients sustain complications of long-term, treatable chronic conditions because of inability to provide the highest quality of care to all patients who enter their doors, regardless of race, ethnicity, culture, class, or language proficiency.

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Anticoagulation in Pregnant Women with Prosthetic Heart Valves

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Abstract

The combination of heart disease and pregnancy can present a formidable challenge to the clinician entrusted to care for both the mother and fetus. Since most data is retrospective, a definitive prognosis for such a patient may be difficult to obtain. Nevertheless, certain cardiac conditions carry greater risks of maternal mortality than do others. However, even for certain preexisting conditions, a tremendous amount of debate persists with respect to risks during pregnancy and optimal peripartum management.

One such area of controversy concerns anticoagulation in pregnant women with prosthetic heart valves. For patients who require anticoagulation for mechanical valves, the choice of some combination of warfarin, unfractionated heparin, and low-molecular-weight heparin (LMWH) has resulted in many small-scale trials, which have not yet provided definite guidance as to the best course of action. Even more controversial has been the recent labeling change that advises against the use of LMWH in all patients with prosthetic heart valves, as a result of two cases of prosthetic valve thrombosis in women using LMWH while pregnant. Although the latest product labeling, in the summer of 2003, was changed to a less restrictive recommendation, debate persists. A discussion of the available data on anticoagulation in pregnant women with prosthetic heart valves is presented here, to inform the clinician and the patient of the risks and benefits of the options presently available.

Key Words: Anticoagulation, pregnancy, prosthetic heart valves.

Normal Physiology of Pregnancy

THE NORMAL HEMODYNAMIC CHANGES that occur during pregnancy may exacerbate underlying cardiac disease. Cardiac output increases 30–50% (1–4) early in pregnancy, due largely to an increase in stroke volume (5). By the third trimester, as venous return diminishes secondary to enlargement of the uterus, with concomitant obstruction of the inferior vena cava and an increase in dilatation of the venous beds, it is the 15–25% increase in heart rate that accounts for the increase in the cardiac output (1). A 15–25% fall in systemic vascular resistance results in either a slight decrease or no change in blood pressure; there is no change in the ejection fraction. A relative anemia results from the 20–30% increase in red blood cell mass that occurs with the 30–50% increase in plasma volume (6). The increased metabolic demands of both the mother and fetus account for the 30% increase in oxygen consumption (1). The increase in arterial and venous capacity may result in an increase in fragility of the vessel wall, which may be partly responsible for the increase in thromboembolic phenomena seen in pregnancy (7–10).

Other hemostatic changes that occur with normal pregnancies involve the coagulation cascade. There is an increase in coagulability of the blood and a decrease in fibrinolytic potential (6). These changes appear to coincide with the development of the uteroplacental circulation. Fibrinogen, factors VII, VIII and X, and von Willebrand factor increase throughout pregnancy. Levels of protein S decrease throughout pregnancy (6). A large study in Sweden found that the incidence of thrombosis was 1.3 per 1000 deliveries; this rate was ten times

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that for nonpregnant women in the same age group (11).

Evaluation of the Pregnant Patient

It is common for a pregnant woman to have some symptoms of cardiac disease, such as fatigue, dyspnea on exertion, palpitations, pedal edema and weakness, all of which may simply result from the normal physiologic changes associated with pregnancy. Common physical findings on examination include a mildly elevated jugular venous pressure, brisk carotid upstrokes, basilar crackles, a laterally displaced point of maximal impulse, a third heart sound, early peaking systolic murmur and peripheral edema. Abnormal findings include cyanosis or clubbing, a loud systolic murmur (>3/6), a diastolic murmur and fixed splitting of the second heart sound (12). If imaging studies are needed, electrocardiogram, echocardiogram, and exercise testing to submaximal levels can be done safely (13). X-ray procedures should be avoided, especially during the first trimester. Radionuclide imaging and catheterization under fluoroscopy should be avoided unless urgently needed (8, 14).

Anticoagulation in Pregnant Women with Prosthetic Heart Valves

Complications in Pregnant Women with Mechanical Heart Valves

Because of the hypercoagulability that results during pregnancy, women with mechanical heart valves are particularly at risk for increased thromboembolic events, with incidence ranging from 7.5–23%. Most such events present as valve thrombosis, with a resultant mortality rate of 40% (11–18). The highest risk of thromboembolism occurs at the mitral position with older mechanical valves (19). Such is the case with the Bjork-Shiley spherical occlude valve, as compared to the Starr-Edwards or St. Jude valves (20). The various methods of anticoagulation will be presented, to determine whether any one method provides superior anticoagulation and/or minimal toxicity to the fetus.

Warfarin

The use of Coumadin (warfarin) in pregnancy is believed to be contraindicated during the first trimester because of the teratogenic effects of the drug, leading to "Coumadin embryopathy syndrome" (21–24). The risk of this syndrome has been estimated at 5–25%; toxic effects result in facial abnormalities, optic atrophy, digital abnormalities, epithelial changes and mental impairment of the fetus. As warfarin crosses the placenta, the fetus is exposed to a disproportionately higher dose than the pregnant woman because of the lack of development of the liver enzymes as well as the low levels of the vitamin-K-dependent clotting factors of the fetus (25). After the first trimester, these clotting factors steadily increase until birth (26). Warfarin should be avoided particularly during weeks 7–12 as evidence suggests that the fetus is most vulnerable to the teratogenic effects of the drug during this time (27).

One study (28) suggests that the effects of Coumadin are dose related. A total of 43 women with prosthetic heart valves who continued taking warfarin throughout pregnancy were followed until term. All of these women agreed to have delivery by caesarian section at week 38, with anticoagulation being stopped two days before the scheduled surgery and continued the day after surgery. The international normalized ratio (INR) was kept between 2.5 and 3.5, and the women were divided into two groups, those who required a dose of 5 mg or less and those who required more than 5 mg of warfarin to maintain the desired INR. Out of a total of 58 pregnancies, there were 31 healthy babies born (30 full-term, one pre-term) with 27 fetal complications (22 spontaneous abortions, 2 warfarin embryopathies, one stillbirth, one ventricular septal defect, one growth retardation). Of the 27 fetal complications, 22 occurred in women taking more than 5 mg of warfarin, whereas only 5 occurred in women taking less than 5 mg of warfarin. No fetal or maternal bleeding was observed during caesarian section or premature vaginal delivery. Two women developed valve thrombosis even with desired levels of anticoagulation; both needed surgery. The incidence of embryopathy in this series was 3.4%, while the abortion rate was 37.5%. The results of this study prompted the authors to suggest that anticoagulation with warfarin at doses less than 5 mg to achieve a therapeutic INR may be safe during the first trimester of pregnancy. Women requiring larger doses of warfarin should be informed of the greater risks of teratogenicity and be given the option of continuing warfarin or substituting subcutaneous heparin during the first trimester.

The editorial comment to the study by Vitale et al. (28) was written by Elkayam (19).

Elkayam noted the important findings but cautioned against the use of warfarin at any dose, because of the small number of patients in the study as well as the fact that, when given the choice of using warfarin in the first trimester, most women prefer not to take it. He recommended that women with first generation prosthetic heart valves in the mitral position, should be informed of the higher risk of thromboembolic events with the substitution of subcutaneous heparin for warfarin in the first trimester, and they should be given the option of using warfarin for anticoagulation, especially those women requiring less than 5 mg to achieve a desired INR. Patients need to be informed of the limited data suggesting that lower doses of warfarin may be safer than higher doses. There is also a risk of litigation. Patients at high risk for development of valve thrombosis should be treated with high doses of subcutaneous or intravenous heparin. If heparin is administered, antifactor Xa levels should be monitored in all of these patients. Because of the high incidence of premature labor in patients with prosthetic heart valves, Elkayam recommends that all such patients be hospitalized at 35 or 36 weeks of gestation and warfarin replaced with heparin.

A retrospective study (29) examined maternal and fetal outcomes in patients who used only warfarin throughout pregnancy (group I, n=42 pregnancies) and patients who substituted subcutaneous heparin in the first trimester with continuation of warfarin afterwards (group II, n=21 pregnancies). Although there were no cases of coumarin embryopathy, spontaneous abortion occurred in 11 fetuses (26.2%) in group I and in 3 fetuses (14.3%) in group II. Although there were no maternal deaths, there were two cases of thrombosed mitral valve prosthesis in group II; both occurred at week 14 (two weeks after heparin had been discontinued and Coumadin started), and both required surgery that saved the patients' lives. Both patients' fetuses aborted afterwards. The authors concluded that, although there are no definitive data for use of anticoagulation, warfarin can probably be safely used throughout pregnancy.

Use of Unfractionated Heparin During the First Trimester

Since warfarin use has been discouraged during the first trimester because of possible teratogenic effects, heparin has been recommended during this time period. Unfortunately, concern over its effectiveness and safety for the mother and fetus remain.

Salazar et al. (18) reported on the use of subcutaneous heparin in 37 women with prosthetic heart valves. All the women received subcutaneous heparin from weeks 6–12 and again in the last two weeks of gestation, with a desired goal of partial thromboplastin time (aPTT) at 1.5–2.5 times the control level. Warfarin was used during all other times. Results included 15 spontaneous abortions in the first trimester (37.5%) without any incidence of coumarin-induced embryopathy; one neonatal death occurred due to cerebral hemorrhage during coumarin therapy. Two women died of fatal massive thrombosis of a mitral tilting-disk prosthesis during the heparin therapy, and one woman died of gastrointestinal bleeding while receiving oral anticoagulation. A total of three thromboembolic events occurred in women with Bjork-Shiley mitral prosthesis. In the discussion, the authors commented that the incidence of spontaneous abortions was 8.8–50% in other studies that used heparin for anticoagulation during the first trimester (30, 31), thus offering little advantage to warfarin therapy in terms of protecting the fetus. There were no thromboembolic events while the women were taking warfarin. In addition, other studies suggest that the use of subcutaneous heparin for prevention of thromboembolic events in the pregnant mother is ineffective (32, 33).

The results of the study by Salazar et al. (18) prompted the authors to recommend that, because there were no advantages to the fetus by substituting heparin for warfarin, warfarin should be used until the 38th week of gestation, with the substitution of intravenous heparin at this time to avoid the use of oral anticoagulation during the last two weeks of pregnancy. The accompanying editorial by Elkayam (34) countered that all studies of pregnant women with prosthetic valves and anticoagulation regimens have been small, but the risk of fetal damage due to Coumadin is well established. Definitive recommendations could not be made, but he suggested that women with older generation prosthetic valves in the mitral position should be informed of the risk of valve thrombosis as well as the dangers of Coumadin embryopathy, to help them decide which form of therapy should be given. In women with older generation valves in the aortic position and those with newer valves in the mitral position, subcutaneous heparin during the first trimester and in the last weeks of gestation should still be recommended. He commented that the aPTT should be kept between 2 and 3 times control value (in a later editorial, he recommends that antifactor Xa levels can also be followed (19)), unlike the minimum of 1.5 times control used by Salazar et al. (18). Finally, it was noted that even the manufacturer of Coumadin has declared the drug to be teratogenic; use by the physician with this knowledge would surely put the practitioner at risk for any ensuing medical legal issues.

The largest review of the use of anticoagulation in pregnant women was reported by Chan et al. (35). The authors included 976 women with 1,234 pregnancies in various studies conducted from 1966–1997. They found that Coumadin embryopathy occurred in 6.4% of live births; if heparin was substituted for warfarin during weeks 6–12 of gestation, this risk could be virtually eliminated. Valve thrombosis occurred in 3.9% of pregnancies when warfarin was used throughout; when heparin was substituted for warfarin in weeks 6–12, valve thrombosis occurred in 9.2% of pregnancies. Maternal risk of death was 1.8% when warfarin was used throughout pregnancy vs. 4.2% when heparin was substituted for warfarin in the first trimester. The authors concluded that the risk of thrombosis was least when warfarin was used, but at the expense of Coumadin embryopathy; use of heparin eliminates this risk, but at the expense of a greater incidence of valve thrombosis and maternal death.

Low-Molecular-Weight Heparin in Pregnant Women

The use of low-molecular-weight heparin (LMWH) as a substitute for warfarin during the first trimester was initially seen as an easy, cost-effective and possibly safer method compared to subcutaneous heparin, given the many reports of thromboembolism with unfractionated heparin. Although there were no randomized, controlled clinical trials to definitively warrant the use of LMWH for this purpose, clinicians seemed to quickly realize the benefits of this alternative. To the surprise of the medical community, however, the pharmaceutical maker of enoxaparin (an LMWH), issued a warning to health care providers discouraging the use of enoxaparin to prevent thromboembolic disease in *any* patient with prosthetic heart valves. Many physicians felt that the real concern of the drug maker was not for pregnant women, given the potential devastating medico-legal consequences for any adverse outcome to the mother or the fetus with enoxaparin. As cause and effect may be difficult to prove or disprove, no such link would need to be made to proceed with litigation. Shortly afterwards, in the summer of 2003, the company mailed letters to physicians stating that LMWH had not been adequately studied in pregnant women with mechanical prosthetic heart valves, thus amending their previous recommendation to avoid its use in all patients with prosthetic heart valves. A review of the history of LMWH and its use in pregnant women and nonpregnant patients with prosthetic heart valves will be briefly presented.

LMWH in pregnant women without prosthetic heart valves. The use of LMWH seemed to be effective in the prevention and/or treatment of deep vein thrombosis in pregnancy in several serial case studies (36–39). Just as important, it was felt that the use of LMWH did not seem to have detrimental effects on the mother or her fetus. A large review (40) done retrospectively of 624 pregnancies treated with enoxaparin reported the following: seven stillbirths, ten serious neonatal hemorrhages, and eighteen major congenital abnormalities, none of which were felt to be due to enoxaparin. Adverse maternal events included eleven cases of bleeding, six of bleeding at delivery, and two of serious maternal thrombocytopenia.

A prospective observational study (41) of low-dose aspirin plus either enoxaparin or heparin in women with recurrent pregnancy loss and antiphospholipid antibody syndrome was conducted with 123 women. Aspirin therapy was initiated immediately, while enoxaparin or heparin was started at 7 weeks and continued until 34 weeks or delivery. With a mean duration of 27 weeks, there were no fetal deaths, bleeding complications, thrombocytopenia, or fractures.

LMWH in nonpregnant patients with prosthetic heart valves. There have been many reports on the use of LMWH, in several clinical settings, in patients with prosthetic heart valves. Its use in periprocedural management was reviewed in a cohort of 1,082 patients (42) who were prophylactically "bridged" from long-term oral coagulation on an outpatient basis. A total of 401 patients had mechanical or bioprosthetic valves, while the remaining 681 patients did not have valves and had other indications for anticoagulation, such as atrial fibrillation, recurrent venous thrombosis, cerebral emboli, transient ischemic attacks and other conditions. The last dose of LMWH was given

12 hours before the procedure, and the first injection was given 8–12 hours following the procedure, after hemostasis was secured. The use of LMWH heparin was overlapped with anticoagulation until a therapeutic INR was reached. The main results were that minor bleeding occurred in 7.6% of patients, major bleeding occurred in 0.27% of patients, and no thromboembolic events were seen in any patient during this bridging period.

In a similar review (43) of periprocedural bridging of 185 patients with mechanical valves, no prosthetic valve thrombosis was observed. Other reports of case series of patients agree that the use of LMWH for "bridging" while off chronic oral anticoagulation was at least as safe as unfractionated heparin, with the additional benefits of shorter length of hospitalization and lower costs (44); the use of LMWH included the immediate anticoagulation after mechanical valve surgery with subsequent administration of warfarin (45–47).

LMWH in pregnant women with prosthetic heart valves. There is very little published data concerning the use of LMWH in pregnant women with prosthetic heart valves. There are case reports or small case series on the use of LMWH in such circumstances, detailing incidences of valve thrombosis (48–51).

The study which led to the controversial labeling change by Aventis (maker of enoxaparin) was to have enrolled 110 patients in a randomized, open-label fashion, comparing enoxaparin with warfarin and unfractionated heparin in pregnant women with prosthetic heart valves (52). But after only 12 patients were enrolled, the safety committee terminated the study due to two deaths from prosthetic valve thrombosis in the enoxaparin group. A detailed report of the circumstances of the deaths of these two pregnant women revealed that one had a prosthetic mitral valve and the other had prosthetic valves in both the mitral and aortic positions. Although recommended therapeutic ranges for Factor Xa are 0.6–1.0 IU/mL (53), the data showed that both women had subtherapeutic levels of Factor Xa just before or at the time of death. As a result, critics of the labeling change believe that the level of anticoagulation with enoxaparin was not optimal and that, given the high risk of adverse outcome with unfractionated heparin in the same clinical setting, such a change was unwarranted and should not be applied to all patients with prosthetic heart valves, even if pregnant.

Current Guidelines: European Society of Cardiology and American College of Cardiology/American Heart Association

The current guidelines by the European Society of Cardiology (ESC) (54) and the American College of Cardiology/American Heart Association (ACC/AHA) (55) recommend the use of warfarin as the anticoagulation of choice for pregnant women with mechanical prosthetic heart valves, for the first 35 weeks of pregnancy (Table 1) (55). The ACC/AHA report also suggests that if women who are at high risk for thromboembolism (history of thromboembolism and/or older generation mechanical prosthesis in the mitral position) choose not to take warfarin during the first trimester, then unfractionated heparin should be given continuously intravenously, with a target of aPTT of 2–3 times control. Women at low risk for thromboembolism who choose not to take warfarin should receive adjusted-dose subcutaneous heparin to achieve a desired aPTT of 2–3 times control. Women who choose not to take warfarin in the first trimester must be made fully aware that unfractionated heparin is less safe for them, with higher risks of both thrombosis and bleeding, than warfarin, and that any risk to the mother also puts the health of the baby at risk.

TABLE 1

Recommendations for Anticoagulation during Pregnancy: Weeks 1 through 35 in Patients with Mechanical Prosthetic Valves

Indication	Class
Whether to use heparin or continue warfarin during the first trimester must be discussed fully with the patient and her partner. If she chooses to use heparin for the first trimester, she must be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.	I
High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the midinterval (6 hours after dosing) aPTT to 2–3 times control. Transition to warfarin can occur thereafter.	I

Adapted with permission from Bonow RO, et al. Guidelines for the management of patients with valvular heart disease. Circulation 1998; 98(18):1949–1984 (55).

After the 36th week of pregnancy (Table 2) (55), the guidelines recommend the cessation of warfarin with the substitution of unfractionated heparin. If warfarin is continued up until delivery, cesarean section should be performed. Finally, once it has been determined that there is no significant bleeding, heparin should be resumed 4–6 hours after delivery and warfarin begun orally.

The ACC/AHA report cautions against the use of LMWH simply because of the lack of data available in the management of pregnant patients with prosthetic heart valves.

Conclusions

Given the lack of data, definitive management of pregnant patients with prosthetic heart valves who need anticoagulation remains particularly challenging. There is, however, general agreement on certain aspects of this entity.

- There is insufficient data to compare or advocate use of warfarin, unfractionated heparin, or LMWH, since there is evidence to suggest that any option or combination of these choices has potentially adverse outcomes for both the mother and fetus. All patients should be advised of the potential risks to the patient and fetus with all options of anticoagulation. The importance of educating the patient on the risks and benefits of each option cannot be overstated; the patient needs to have this information to make a decision with which she is most comfortable.
- ACC/AHA guidelines recommend that warfarin be used as the choice of anticoagulation in weeks 1–35, since there is evidence to show that use of unfractionated heparin as a substitute early on increases the risk of harm to the mother; at week 36 and afterwards, heparin may be used instead of warfarin, but if warfarin is continued, caesarian section is recommended at the time of delivery to avoid excessive bleeding (55).
- ACC/AHA guidelines recommend that patients who choose not to take warfarin during the first trimester, and patients who are at high risk for thromboembolism (history of previous thromboembolic disease or older generation prosthetic valve at the mitral position) should receive intravenous unfractionated heparin with a target aPTT of 2–3 times control. Patients who are at low risk should receive subcutaneous heparin with a target aPTT of 2–3 times control (55).
- There is insufficient data as to the use of LMWH in pregnancy (55).

TABLE 2
Recommendations for Anticoagulation during Pregnancy: After the 36th Week, in Patients with Mechanical Prosthetic Valves

Indication	Class
Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.	IIa
If labor begins while the patient is still on warfarin, a cesarean section should be performed.	IIa
In the absence of significant bleeding, heparin can be resumed 4–6 hours after delivery, and warfarin begun orally.	IIa

Adapted with permission from Bonow RO, et al. Guidelines for the management of patients with valvular heart disease. Circulation 1998; 98(18):1949–1984 (55).

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Acute Myocardial Infarction and Left Subclavian Artery Occlusion in Behçet's Disease:

A Case Report

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Abstract

A 42-year-old woman with Behçet's disease and pericardial effusion for 14 years presented with acute myocardial infarction and received thrombolytic therapy. Coronary angiography showed total occlusion of the left anterior descending artery. Subsequently, the left internal mammary artery was grafted to the left anterior descending artery. Approximately one year after bypass surgery, digital subtraction angiography of the left subclavian artery, performed because of chest and left arm pain, showed total occlusion of the left subclavian artery. Retrograde flow from the left vertebral artery filled the distal portion of the left subclavian artery.

In conclusion, patients with Behçet's disease should be investigated closely for involvement of other arteries when one vessel's involvement has been detected. We also recommend that free arterial grafts be used for any coronary surgical intervention, because of the risk of occlusion associated with the vasculitis of Behçet's disease.

Key Words: Behçet's disease, myocardial infarction, vasculitis, subclavian artery occlusion.

Introduction

BEHÇET'S DISEASE is a recurring systemic vasculitis of unknown etiology which can affect all bodily systems. In 1937, Hulusi Behçet, a dermatologist, first described the disease as a triad of oral and genital ulceration and ocular lesions. Cardiac involvement, known as cardio-Behçet's disease (1), has also been reported, although it is very uncommon. In such cases, reported symptoms have included thrombus formation in both right atrium and right ventricle, tricuspid regurgitation, coronary aneurysm and acute myocardial infarction (MI) due to coronary artery involvement (2–4).

In this case report, Behçet's disease was diagnosed in a 28-year-old woman who developed recurrent pericardial effusion and later had an acute MI because of the occlusion of the left anterior descending artery (LAD). Subsequently, after a long follow-up period, the origin of the left subclavian artery became occluded.

Case Report

A previously healthy, 28-year-old woman presented in 1988 with pain and burning sensation in both inguinal regions and with red swellings on her legs. A punch biopsy of the involved skin revealed erythema nodosum. These lesions also occurred on both the anterior and posterior sides of the left arm; they disappeared after steroid therapy. Multiple recurrent aphthous ulcerations were found on the buccal mucosa under the tongue and on the lips. These ulcerations were successfully treated with topical steroids in the form of a paste.

In 1996, the patient was hospitalized because of extensive lesions on her skin and general poor health. In addition, both eyes were involved, and visual acuity in her left eye had rapidly diminished to near-blindness. Physical examination revealed thrombosis in the left retinal artery. Methylprednisolone (1 mg/kg) was initiated, and photocoagulation was performed. Ocular findings disappeared within three months. Steroid therapy was discontinued

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and colchicine therapy (1 mg/day) was started. At this point, a pathergy test was performed, as follows: an injector needle was inserted deeply (up to 2–4 mm) three times at a 45° angle into the right forearm and three times at a 90° angle into the left arm of the patient; all insertion places were marked circumferentially with a pen. A positive test was indicated by the appearance of four papulopustular lesions after 72 hours. Behçet's disease was diagnosed, based on the recurrent oral aphthous ulcers, erythema nodosum, ocular findings and positive pathergy test.

One year later, the patient was readmitted with the complaint of progressive fatigue while on colchicine therapy. Physical examination revealed that her lesions were reactivated. The patient was referred for cardiac evaluation. ECG and chest X-ray were normal, whereas diastolic dysfunction of the left ventricle and minimal pericardial effusion were observed on echocardiographic examination. Laboratory test results were as follows: hematocrit value, 37% (normal 37–47%); white blood cell, 8,000/mm^3 (normal 4,800–10,800); platelet count, 250,000/mm^3 (normal 150,000–400,000); erythrocyte sedimentation rate, 17 mm/h (normal < 20); C-reactive protein 12 IU (normal < 6); rheumatoid factor, 5 IU (normal 0–15); antinuclear antibodies, negative; and histocompatibility antigen HLA-B5, positive.

In August 2000, she was admitted to our coronary care unit (CCU) after a 30-minute episode of pressure-like chest pain. Serial ECGs demonstrated ST segment elevation in leads V_{1-4} and reciprocal changes in leads II, III, and aVF; acute anteroseptal MI was diagnosed (Fig. 1). The creatine phosphokinase (CPK-MB) was 26 IU/L (normal < 24) on admission and increased to 148 IU/L after 8 hours This increase confirmed the diagnosis of acute MI. Her blood pressure was 80/50 mm Hg and her heart rate was 85 bpm. Tissue-plasminogen activator (t-PA) was chosen for thrombolytic therapy because of severe hypotension. Ten minutes after t-PA administration, nonsustained ventricular tachycardia occurred. Amiodarone infusion was started because of lack of response to lidocaine, and the episodes of ventricular tachycardia stopped. When the patient developed severe hypotension (50/30 mm Hg), dopamine and dobutamine infusions were started. She responded well to inotropic therapy and stabilized after two hours. Her heart rate continued to be rapid (106–125 bpm) for two days. At that time, complete blood count, prothrombin time (1.32 INR), and activated partial thromboplastin time (39 seconds, normal 28–40) were within normal limits. Levels of plasma fibrinogen (218 mg/dL, normal 200–400), factor VIII and factor V were also normal. Platelet structure and function tests (platelet aggregation, adenosine diphosphate [ADP], collagen and epinephrine levels) were within normal limits. Plasma lipid values were as follows: triglyceride, 133 mg/dL; total cholesterol, 206 mg/dL; HDLchol, 42 mg/dl; LDL-chol, 137 mg/dL. Fasting blood sugar was 87 mg/dL. Anticardiolipin antibodies immunoglobulin M (IgM) and lgG were negative. Plasma total homocysteine level was 10.70 mol/L (normal 7.83–9.54 for females). The patient was subsequently discharged.

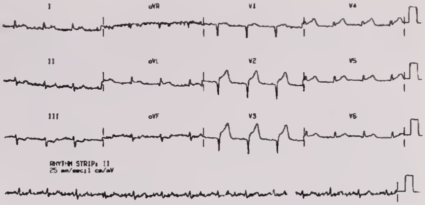

Fig. 1. Admission electrocardiogram presenting typical anteroseptal myocardial infarction.

In September 2000, coronary angiography showed total occlusion of LAD after the first diagonal artery. Other coronary vessels were normal. Left ventriculography demonstrated anterolateral and anteroapical hypokinesia. It was decided that a coronary bypass operation might help restore flow to the LAD. To exclude a pre-existing subclavian stenosis, a presurgical subclavian angiogram was performed; it showed normal vessel anatomy.

One week later, the patient's left internal mammary artery (LIMA) was grafted to her LAD. There was no gross pathologic appearance in the LIMA. The histologic findings in the LAD revealed inflammation consistent with chronic vasculitis; there was no specific evidence of atherosclerosis. No complication was observed in the immediate postoperative period.

In February 2001, the patient presented again with a 10-day history of shortness of breath, nausea and vomiting. Physical examination was normal. Chest X-ray showed an enlarged heart with prominent left ventricular shadow. ECG showed pathologic Q waves in leads V_{1-3} and T inversion in leads V_{2-6}.

Echocardiographic examination showed minimal mitral insufficiency, apical hypokinesia and pericardial effusion; the ejection fraction of the left ventricle was 54%. Administration of indomethacin, 200 mg daily, was begun for pericardial effusion. Because shortness of breath and chest pain persisted, coronary angiography was performed. Left internal mammary artery flow was observed to be normal by selective catheterization of left subclavian artery.

In October 2001, the patient was readmitted because of pain in both arms and in her chest, especially while exercising. On physical examination, left brachial artery and its lower pulses were nonpalpable. Aortography was performed for nonpalpable pulses and revealed total occlusion of the left subclavian artery. During digital subtraction angiography, injection of contrast material into the right subclavian artery resulted in visualization of the right subclavian artery, the right carotid arteries, and in the late phase, the left vertebral artery. Blood flow to the left subclavian artery came from the left vertebral artery (Fig. 2). The distal portions of the left subclavian and axillary arteries were normal. Also, it was noticed that the segment of right internal carotid artery distal to the posterior communicating artery was stenotic. A saphenous vein graft was placed between the left and right subclavian arteries. On ultrasound examination one month later, flow was noted to be decreased in the left subclavian artery while normal in the right axillary artery. The patient's symptoms diminished. The patient is still being followed.

Discussion

Behçet's disease is a systemic multisystem vasculitis. It is estimated that the rate of vascular involvement in Behçet's disease varies from 7–29% (5). Vascular involvement is divided into three groups: venous and arterial occlusions and aneurysm formation (6). Large arterial lesions are infrequent in Behçet's disease. Large artery involvement occurs in 1.5–2.2% of all patients with Behcet's disease (7).

Acute MI is most often the result of atherosclerotic coronary artery disease. But in young adults with acute MI, nonatherosclerotic etiologies such as arteritis, trauma, embolization, dissection, spasm and congenital anomalies should initially be considered. Coronary artery involvement is very rare in Behçet's disease. To the best of our knowledge, only a few cases diagnosed in males were reported as MI in the lit-

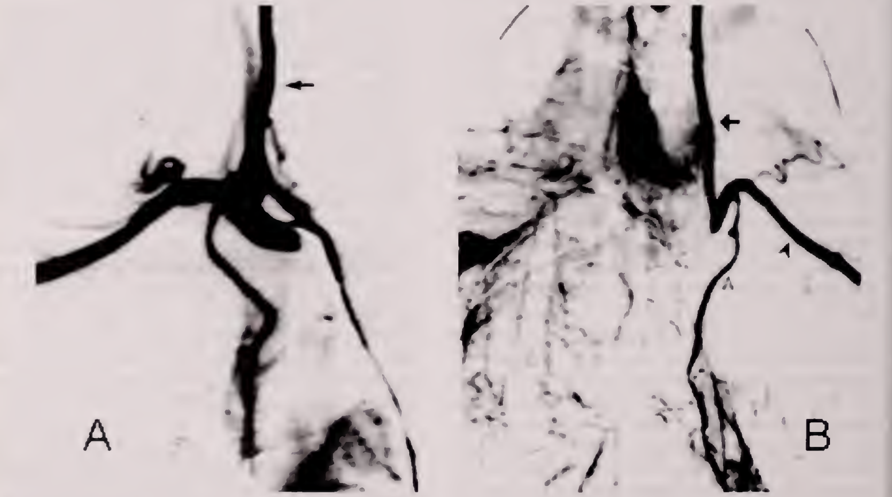

Fig. 2. **(A)** Digital subtraction angiography of right subclavian artery. Arrow shows right carotid artery. **(B)** Late phase angiogram shows retrograde flow into left vertebral artery (arrow); dark and open arrowheads reveal left subclavian artery and left internal mammary artery, respectively.

erature (4, 8, 9). This female case is the first report of combined lesions of the coronary artery presenting with acute anterior MI. Peripheral artery involvement included retinal artery thromboses (with blindness) and subclavian artery thrombosis.

Schiff et al. (4) reported a 31-year-old male diagnosed with Behçet's disease. This patient, with a family history of only coronary heart disease and without any history of diabetes mellitus, hypertension, hyperlipidemia or smoking, was first diagnosed with MI. His coronary angiography showed total occlusion of the LAD, as in our case. Following an episode of pericarditis, he experienced multiple cardioversions for ventricular tachycardia and fibrillation, and died due to ventricular tachycardia. Postmortem examination revealed marked fibrosis with aneurysmal dilatation of the apex and anterior half of the left ventricle. Examination of LAD demonstrated complete proximal occlusion by an organized thrombus, and distally a transmural sclerotic process, which partially destroyed the elastic layer and adventitia. It was suggested that such a transmural sclerotic process was consistent with arteritis due to Behçet's disease, because there was no finding suggestive of atherosclerosis.

A second case presenting with acute anteroseptal MI was a 34-year-old man with no known coronary risk factors. This was also considered a consequence of coronary arteritis instead of coronary atherosclerosis and embolism (8).

One of the other cases of coronary involvement, but not presenting as acute MI, was a 35-year-old Japanese housewife with Behçet's disease. She complained of pain in the epigastrium, right anterior chest and right shoulder. Her coronary angiogram demonstrated a vascular aneurysm of the proximal right coronary artery as well as two obstructive lesions (10). Bowles et al. (11) reported a 22-year-old woman who presented with acute MI, and had dilatation of the LAD and occlusion of the septal coronary artery. Siepmann and Kirch (9) recently reported a young man who had complete occlusion of the circumflex branch in the proximal part and a convoluted fistula from the left main branch to the pulmonary artery. Gullu et al. (12) described a silent myocardial ischemia in Behçet's disease that was probably due to microvascular vasculitis in the intramyocardial small arteries.

The common features of all venous and arterial histologic abnormalities include largely lymphocytic and plasma cell infiltration, disrupted internal elastic lamina, aneurysms, occlusive thromboses and variously aged lesions (from fresh vasculitis to fibrotic replacement) of previously occluded vessels (13, 14).

Our patient had a history of smoking 10 cigarettes daily for several years. There was no family history of coronary artery disease and no other risk factors, such as hypercholesterolemia, hypertension, diabetes, or high plasma homocysteine level for atherosclerosis. We concluded that there were two etiologic reasons why acute MI in our patient was arteritis instead of atherosclerosis. First, there was no evidence of atherosclerosis in the biopsies of the LIMA and LAD obtained at operation. Second, the patient had no risk factors for coronary artery disease and there was no evidence of any atherosclerotic process. Subsequently, total occlusion of the subclavian artery occurred after an acute MI. Some authors think that elevated clotting factors such as platelet count, factor VIII, and fibrin split products appear to be the result and not the cause of the vasculitis (15). As with other idiopathic inflammatory diseases that affect endothelial cells, coagulation abnormalities in Behçet's disease, due to defective release of t-PA, are probably a secondary phenomenon (16). Our patient suffered from blindness, probably due to retinal artery thromboses. As previously reported, thrombotic occlusion may be a risk factor for acute MI.

Two points from the literature should be noted. First, coronary involvement is more common in men than in women (9), whereas the reverse is true for vascular involvement (17). Second, the coronary artery most often involved in Behçet's disease is the LAD.

This case has demonstrated that Behçet's disease should be investigated closely in terms of the heart and vessels, especially when symptoms develop which suggest impairment of flow. We propose that internal mammary artery or radial artery grafts should be used for coronary by-pass operation in the setting of Behçet's disease, because of the probability of occlusion of large arterial vessels such as the subclavian artery.

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Physicians' Religiosity and End-of-Life Care Attitudes and Behaviors

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Abstract

Background: Physicians play the central role in decisions to initiate, withhold and withdraw life-sustaining medical care. Prior studies show that physicians' religiosity is related to end-of-life care attitudes and practices, which — if not in concert with the patient or family — may be a source of conflict. We surveyed physicians of one religion to describe the relationship between religiosity and end-of-life care.

Methods: Cross-sectional survey of 443 Jewish physicians at four Israeli hospitals, which characterized religiosity and asked about attitudes and communication with patients about end-of-life issues and care practices.

Results: Very religious physicians, compared to moderately religious and secular physicians, were much less likely to believe that life-sustaining treatment should be withdrawn (11% vs. 36% v. 51%, $p<0.001$), to approve of prescribing needed pain medication if it will hasten death (69% vs. 80% vs. 85%, $p<0.01$), or to agree with euthanasia (5% vs. 42% vs. 70%, $p<0.001$). Religiosity was not related to withholding most life-sustaining treatments, but even after adjustment for physician and practice characteristics, very religious physicians were much less likely to "ever stop life-sustaining treatment provided to a suffering terminally ill patient" ($p<0.0003$). Religiosity was unrelated to physician-patient communication or to desire for support concerning end-of-life care. Desire for support was universally high.

Conclusions: Physicians' religiosity can have a major effect on the way their patients die, including whether patients receive adequate analgesia near death. Patients may need to query physicians' religious perspectives to ensure that they are consistent with patients' end-of-life care preferences. Evaluation of religiosity-related clinical behavior in other cultures is needed.

Key Words: End of life decisions, physician behavior, religion, terminal care.

Introduction

DECISIONS ABOUT THE END OF LIFE, such as whether to pursue aggressive care or withhold or withdraw life-sustaining treatments, require consideration of clinical factors in the context of a patient's values. These decisions are complex, varying substantially across cultures (1–3). Physicians play the central role in decisions to initiate, withhold and withdraw care. Beyond clinical circumstances, physicians' decisions also are influenced by cultural, personal and practice factors that affect physicians' perceptions of the proper course for care. Such influences, if not in concert with those of the patient and the patient's family, can be a source of conflict regarding end-of-life care (4, 5).

The one physician characteristic that is most consistently related to end-of-life care attitudes and behaviors is level of religious commitment. Other physician demographic factors have been shown to be related to end-of-life care in some studies, but not in others. Physician gender, for example, is related to communication with patients (6), but not to withholding and withdrawing treatments in neonates (1), or accepting (7, 8) and performing (9) euthanasia. Gender is also not related to attitudes concerning appropriate end-of-life care among medical students (10). Similarly, physician age and professional experience have been shown to be related to terminal care practices and attitudes in some studies (1, 7, 11), but not in others (8, 9). Furthermore, several studies found no relationship when comparing end-of-life behaviors and attitudes with provider practice

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characteristics, such as practice type (1), specialty (7, 9, 12), size (9) and geographic region (8, 9). Contrary to these presumably weak influences, religious influence is consistently strongly related to physician-reported end-of-life attitudes and behaviors (1, 7–12). However, studies of the influences of physician end-of-life attitudes and behaviors usually include religion only as a covariate. Health researchers have not focused on understanding the role of physicians' religious beliefs on end-of-life attitudes and care practices. Specifically, how does religion affect a physicians' communication with patients about end-of-life care? And does a physician's religiosity influence use of analgesics, withholding and withdrawing behaviors, and views toward euthanasia?

Furthermore, most studies of physicians include a variety of religions. However, since there is considerable variation in the relationship between type of religion and end-of-life attitudes and behaviors (7–9), we endeavored to understand the relationship of religiosity and end-of-life care attitudes and behaviors in a sample of physicians adhering to only one religion. We surveyed Israeli Jewish physicians whose religiosity covered a wide range. Focusing on Israel, where a paternalistic bent means that physician perspectives may be even more influential in care decisions than in other Western countries (13), we attempted to understand the depth and breadth of the effect of religiosity on end-of-life communication, attitudes and behaviors.

Methods

We conducted a cross-sectional survey of physicians in four hospitals in Israel. Attending physicians and residents at these institutions were eligible for the survey if they practiced in the fields of internal medicine, family medicine, geriatrics, oncology, critical care or surgery. Data were collected in two waves: at two hospitals physicians completed surveys from June to November 1997 and at the other institutions December 1998 and March 1999. Of the 615 physicians approached for participation in the study, 443 completed the survey, for an overall response rate of 72%.

Survey Instrument Design

The survey instrument was constructed on the basis of the literature, clinical experience and an earlier exploratory investigation conducted at one of the hospitals (14). The self-administered survey instrument, which was completed in Hebrew, asked about: treatment intentions using hypothetical scenarios, communication concerning end-of-life care, attitudes about end-of-life treatments, end-of-life care practices, factors influencing a physician's end-of-life decisions, and the physician's demographics, professional characteristics, religiosity and type of practice.

Religiosity was measured using a five-item scale, which is a short version of the Jewish Religiosity Scale (15). The items asked about strength of religious belief, participation in religious ceremonies or prayers, self-perceived religiosity, religiosity of the home in which the respondent was raised, and whether the respondent adhered to Jewish dietary laws. Factor analysis revealed that these items form a single construct with an internal consistency of 0.88. The items are summed into an index with a theoretical range of 5–25, with a higher score indicating greater religiosity. Other physician characteristics queried in the survey included: age, gender, marital status, number of children, place of birth, year of immigration to Israel, years in practice, specialty, whether the physician was an attending or a trainee, and whether the physician had a managerial role and held an academic title.

Respondents were asked about their treatment intentions regarding four treatment modalities: hydration, tube feeding, mechanical ventilation and cardiopulmonary resuscitation (CPR). The scenario presented the following patient: "A cancer patient of about 80 years old presents to you, without a family, with severe metastatic cancer with a prognosis for only temporary improvement." Physicians were asked:

- If he cannot eat, would you provide fluids?
- If he cannot eat, would you connect him to artificial feeding (nasogastric tube or gastrostomy)?
- If he cannot breathe, would you connect him to a breathing machine?
- If his heart stops beating, would you perform CPR?

Response options were presented using a 5-point scale ranging from 1 ("certainly would not") to 5 ("certainly would"). Physicians then were asked an analogous question about themselves: "If you had severe metastatic cancer and treatment could afford only temporary improvement...." The same questions and response options were presented for the respondent to consider personal treatment desires.

Attitudes and behaviors toward end-of-life care were explored by asking about withdrawing care; provision of analgesics, even if it would shorten life; and active euthanasia. A dichotomous response option was provided for these questions. Physicians also were asked about their level of support for active euthanasia, based on the synopsis of a published case (16), using a 5-point scale ranging from "complete support" to "firm opposition."

End-of-life care practices and practice intentions were evaluated with items asking whether the physician initiates withdrawal of life-sustaining treatment; whether the physician would comply with the request of a competent, continuity patient with a terminal condition who requests euthanasia; and whether he or she would accept the directives in a living will.

Attitudes concerning communication about end-of-life care were probed with items asking whether physicians should: inform a patient about a metastatic cancer diagnosis; inform a patient approaching death about prognosis; and discuss life-sustaining treatment preferences in advance of need. Two items elicited perceptions about whether patients close to death desire information about their condition and whether they desire to participate in treatment decisions. Three items asked about communication behaviors, specifically whether the physician discloses prognosis to a patient who is close to death and whether the physician consults with patients about treatment preferences.

Physicians were asked about the factors that influence whether they initiate life-sustaining treatment for a patient with an irreversible terminal condition. These items queried the influences of physicians' duties, laws and policies, patients' and families' wishes, and religious beliefs using a 1 (not at all) to 5 (a great extent) scale. Lastly, physicians were asked about whether they perceived a need for support and guidance concerning the treatment of dying patients.

Analysis

The religiosity scale demonstrated a range of 5 – 24. It was generally normal in distribution but had a broad group at the lower extreme. Non-religious physicians were defined as those with scores below 6, moderately religious physicians were those with scores between 6 and 15, and very religious physicians had scores above 15. This religiosity variable was used to perform bivariate analyses of attitudes and behaviors concerning end-of-life care. In addition, physician demographic and practice characteristics were evaluated with respect to religiosity. Chi square tests and one-way analysis of variance were used, when appropriate, to compare each variable across the three religiosity categories. T-tests and chi square tests and Fisher exact tests, as appropriate, were used to perform comparisons among the three pairs of groups.

To evaluate the independent contribution of religiosity to the behavior most likely to have a clinical effect on patients, we evaluated physicians' reported frequency of withdrawing life-sustaining treatment from a patient, using linear regression. In addition to religiosity, which was included as a continuous variable, we incorporated independent physician variables that were significantly associated with religiosity in this study and physician characteristics associated in the medical literature with end-of-life care behaviors including: physician's age, gender, place of birth (Israel versus elsewhere), whether an immigrant since 1989, medical specialty (internal medicine vs. surgery) and professional status (attending vs. generalist vs. a physician-in-training).

Results

The sample of 443 physicians had a mean age of 41 years, 88% were married and they had, on average, two children. Seventy percent were men, nearly half were born in Eastern Europe and 36% in Israel. About two-thirds of these physicians practiced or were training in internal medicine or a medical specialty (Table 1).

The mean score on the religiosity scale, which ranges from 5 – 25, was 9.2 (median 8.0 and standard deviation 4.2). Thirty-two percent (141) of physicians were categorized as "secular," 59% (262) as "moderately religious" and 9% (40) as "very religious." This corresponded well with the single item that requested self-classification of religiosity: 70% "completely non-religious," 21% "traditional," 7% "religious" and 2% "very religious." Religious physicians, compared to less religious physicians, were somewhat older, had more children, and were less likely to have been born in Eastern Europe or have immigrated in the past decade. Consistent with being older, they had spent more years in medical practice and were less likely to be in training or general practitioners (Table 1).

End-of-Life Attitudes and Practices

Physicians who were more religious described attitudes and practices concerning end-of-life care that were protective of length of life. There was consistency between attitudes and with respect to withdrawing care and be-

TABLE 1

Socio-demographic and Professional Characteristics of Three Groups of Israeli Physicians: Very Religious, Moderately Religious and Not Religious

	Not Religious (n=141)	**Moderately Religious (n=262)**	**Very Religious (n=40)**	**Total Sample (n=443)**
Socio-demographic characteristics				
Age, mean (SD)	**40.9 (8.1)***	**40.7 (8.4)†**	**45.3 (10.8)*†**	41.2 (8.7)
Married or live with partner (%)	87.2	87.8	94.9	88.3
Number of children, mean (SD)	**2.0 (1.3)***	**1.9 (1.1)†**	**3.6 (1.9)*†**	2.1 (1.4)
Male (%)	70.9	69.3	75.0	70.3
Place of birth (%)				
Israel	**38.6***	**34.4†**	**41.0*†**	36.4
America and West Europe	**12.1**	**8.4**	**28.2**	11.0
East Europe	**48.6**	**54.0**	**28.2**	49.9
Asia and North Africa	**0.7**	**3.2**	**2.6**	2.3
Immigrated since 1989 (%)	**38.3***	**42.0†**	**17.5*†**	38.6
Professional characteristics				
Years in practice, mean (SD)	**14.1 (8.2)***	**14.2 (9.0)†**	**18.3 (11.3)*†**	14.6 (9.1)
Academic rank (%)	43.7	38.4	48.6	41.1
Specialty (%)				
General medicine	**59.5***	**68.2†**	**86.8*†**	32.8
Surgery	**40.5**	**31.8**	**13.2**	67.2
Professional status*				
General practitioner or resident	**44.0**	**54.0†**	**35.0†**	49.0
Specialist	**56.0**	**46.0**	**65.0**	51.0
Managerial status (%)	18.4	13.4	25.6	16.1

SD = standard deviation

Values in **BOLD** are significantly different across the three groups at p<0.05.

*p<0.05 for comparison between Not Religious and Very Religious groups.

†p<0.05 for comparison between Moderately Religious and Very Religious groups.

tween attitudes and behavioral intervention with respect to euthanasia. However, with regard to withholding care, the relationship between religion, attitude and behavioral intent was more complex. Concerning provision of life-sustaining treatment to an older, terminally ill man with cancer, there was no statistically significant difference by religiosity concerning hydration, tube feeding and mechanical ventilation. However, very religious physicians were less likely to withhold CPR (p<0.01). When considering the same treatment modalities for themselves, if they were to have metastatic cancer, very religious physicians' responses were consistent with the care intended for the terminally ill 80-year-old man. However, less religious physicians were less likely to desire for themselves the treatment modalities that they would provide to the hypothetical 80-year-old terminally ill man. This divergence between personal attitude and behavioral intention resulted in very religious physicians desiring for themselves more life-sustaining treatment then did their less religious counterparts (all p's<0.05), whereas care intentions for the 80 year old man, with the exception of CPR, reflected no difference by religiosity (Table 2).

With regard to withdrawing treatment, very religious physicians were less likely than moderately religious or secular physicians to agree that there are circumstances in which a life-sustaining treatment should be withdrawn (11% vs. 36% vs. 51%, respectively, p<0.001). Consistent with this view, very religious physicians were much less likely to report that they had withdrawn life-sustaining treatment from a patient (p<0.01). While non-religious physicians were more likely than moderately religious physicians to agree that there are circumstances in which life-sustaining care should be stopped, there was no significant difference between these groups in reported behavior. Concerning euthanasia, very religious physicians were less likely to approve, in principle, the use of a lethal injection to end a terminal patient's life, to approve of the euthanasia act in the "Debbie" case, or to be willing to perform euthanasia if requested by a patient (all p<0.01) (Table 2).

TABLE 2

Relationship of Religiosity and End-of-Life Care Attitudes and Behavior Among Israeli Physicians

	Not Religious (n=141)	Moderately Religious (n=262)	Very Religious (n=40)	Total Sample (n=443)
Attitudes				
Would you prefer the following life-sustaining treatment if you were terminally ill with metastatic cancer?[a] Mean (SD)				
Hydration	**3.63 (1.7)***	**3.82 (1.6)**	**4.28 (1.1)***	3.80 (1.6)
Tube feeding	**2.51 (1.6)***	**2.62 (1.6)†**	**3.43 (1.5)*†**	2.66 (1.6)
Mechanical ventilation	**1.52 (1.1)***	**1.63 (1.2)†**	**2.31 (1.6)*†**	1.66 (1.2)
Cardiopulmonary resuscitation	**1.32 (0.9)***	**1.38 (1.0)†**	**2.15 (1.6)*†**	1.43 (1.1)
Are there situations in which the use of a life-sustaining treatment (such as mechanical ventilation and dialysis) should be stopped after it was begun?[b] (%)	**50.7*‡**	**36.3†‡**	**10.8*†**	38.8
Do you approve of prescribing for a terminally ill patient a pain medication, even if it will shorten his life?[b] (%)	**84.7***	**80.2**	**69.4***	80.7
In principle, should a physician perform euthanasia if the patient requests it?[b] (%)	**70.3*‡**	**42.2†‡**	**4.5*†**	44.0
Do you approve of the physician performing euthanasia in the Debbie case?[a] Mean (SD)	**3.00 (1.5)***	**2.72 (1.4)†**	**1.59 (1.1)*†**	2.71 (1.4)
Behavior and Behavioral Intention				
Would you order the following life-sustaining treatment for an 80-year-old terminally ill cancer patient?[a] Mean (SD)				
Hydration	4.55 (0.9)	4.65 (0.8)	4.57 (0.8)	4.61 (0.9)
Tube feeding	3.38 (1.6)	3.52 (1.5)	3.37 (1.5)	3.46 (1.5)
Mechanical ventilation	2.17 (1.4)	2.29 (1.5)	2.35 (1.6)	2.26 (1.5)
Cardiopulmonary resuscitation	**1.53 (1.1)***	**1.73 (1.2)†**	**2.25 (1.6)*†**	1.71 (1.2)
Do you ever stop life-sustaining treatment provided to a suffering terminally ill patient?[a] Mean (SD)	**2.59 (1.2)***	**2.41 (1.1)†**	**1.95 (1.0)*†**	2.43 (1.1)
If a patient you know well who has a terminal condition and is cognitively functioning requests that you perform euthanasia, would you comply with his request? [b] (%)	**35.3*‡**	**22.2†‡**	**0.0*†**	22.0
Will you comply with a patient's living will that requests withholding of life-sustaining treatment? (%)				
Yes, always	**62.3*‡**	**49.8†‡**	**36.1*†**	52.7
Yes, with reservation	**21.8**	**26.3**	**50.0**	26.8
No	**15.9**	**23.9**	**13.9**	20.5

SD = standard deviation

Values in **BOLD** are significantly different across the three groups at $p<0.05$.

*$p<0.05$ for comparison between Not Religious and Very Religious groups.

†$p<0.05$ for comparison between Moderately Religious and Very Religious groups.

‡$p<0.05$ for comparison between Not Religious and Moderately Religious groups.

[a] Responses on 5-point scale ranging from 1 (certainly would not) to 5 (certainly would).

[b] Response of "yes" to dichotomous choice.

Concerning acceptance of a living will, very religious physicians were more likely to accept the preferences "with reservation" whereas less religious physicians reported that they would permit such documents to guide care without restriction (Table 2).

The multivariate linear regression model predicting whether a physician withdraws care from patients showed that less religiosity ($p=0.0003$) and practicing internal medicine rather than surgery ($p<0.0001$) were independently associated with withdrawing life-sustaining care. Physician age, gender, birth country, immigration status and professional status were unrelated to withdrawing care.

Little variation by religiosity was detected with regard to communication about end-of-life care. Very religious physicians were slightly less likely than moderately religious physicians to agree that physicians should prospectively discuss end-of-life issues with patients ($p<0.05$). However, there was no significant difference in views concerning whether a physician must inform a patient about a terminal cancer diagnosis, whether a physician must disclose to a patient that he or she is close to death, or whether patients want precise information or to participate in decisions about the end of life. The similar attitudes translated into similar reported behaviors with regard to informing patients that they are close to death and discussing preferences and treatments with patients (Table 3).

Factors Influencing End-of-Life Treatment Decisions

More religious physicians were more likely to report that their behavior in treating a terminally ill patient was influenced by their personal religious beliefs ($p<0.001$), the patient's religious beliefs ($p<0.05$), and the belief that the physician has a duty to prolong life ($p<0.001$).

TABLE 3

Relationship of Religiosity to End-of-Life Communication Among Israeli Physicians

	Not Religious (n=141)	Moderately Religious (n=262)	Very Religious (n=40)	Total Sample (n=443)
Communication Attitudes				
The physician must talk with the patient about his wishes regarding life-sustaining care so these wishes can be considered when needed.[a] Mean (SD)	**3.74 (1.2)**	**3.88 (1.1)**[†]	**3.45 (1.3)**[†]	3.79 (1.1)
If a patient has metastatic cancer with no chance of cure, should the physician tell the patient?[b] (%)	70.7	71.5	76.3	71.7
A patient should be informed of their prognosis as they approach death.[a] Mean (SD)	3.09 (0.9)	3.06 (1.2)	3.31 (1.1)	3.09 (1.1)
Patients who are close to death desire precise information about their condition.[a] Mean (SD)	3.03 (0.9)	2.99 (0.9)	3.26 (0.8)	3.03 (0.9)
Patients desire to participate in treatment decisions regarding limiting treatment.[a] Mean (SD)	3.19 (0.9)	3.13 (0.9)	3.45 (0.7)	3.18 (0. 9)
Communication Behaviors				
Do you tend to tell your patient about his prognosis, even if he is close to death?[a] Mean (SD)	2.62 (1.1)	2.65 (1.2)	2.60 (1.2)	2.64 (1.2)
Do you tend to find out what the patient wants regarding prolonging his life?[a] Mean (SD)	3.19 (1.3)	3.22 (1.3)	3.25 (1.3)	3.21 (1.3)
Do you consult with patients with terminal diagnoses about their treatment?[a] Mean (SD)	3.26 (1.3)	3.33 (1.6)	3.41 (1.1)	3.32 (1.2)

SD = standard deviation

Values in **BOLD** are significantly different across the three groups at $p<0.05$.

[†] $p<0.05$ for comparison between Moderately Religious and Very Religious groups.

[a] Responses on 5-point scale with a higher score indicating more agreement with the statement.

[b] Response of "yes" to dichotomous choice.

But, more religious physicians were less influenced by the belief that a doctor must prevent suffering. Very religious physicians were less likely to report being influenced by the law or hospital ward policies. No significant differences were found among the three groups concerning regard for patients' and families' wishes in making end-of-life decisions (Table 4).

Perceptions of need for aid in the provision of end-of-life care were similar across religiosity groups, but very religious physicians perceived less of a need for additional guidance at the legal level. All groups expressed a high level of desire for support groups concerning the treatment of dying patients.

Comments

There is increasing interest in the importance of religion in health and the provision of medical care. There are suggestions that religious observance is associated with improved clinical outcomes (17), that some patients are interested in their physicians interacting with them on a religious level (18), and that physicians who attend to spiritual and religious concerns might grow both as individuals and practitioners (19). Physicians' recognition of the importance of spirituality in a patient's life may enhance the physician-patient relationship and the benefits of medical care, particularly at the end of life. However, we present data that demonstrate another effect of religion at the end of life: Physician religiosity may translate into different end-of-life care. Not only were the attitudes of very religious physicians different than those of their less religious counterparts, but very religious physicians reported withdrawing care from their patients less often. While this finding previously has been shown concerning neonates in a cross-cultural context (1), the data presented here derive from a homogenous cohort of physicians, suggesting that the end-of-life care a patient receives will vary based on the religiosity of his or her physician.

TABLE 4

Relationship of Religiosity to Factors Influencing Physicians' End-of-Life Treatment Decisions and Perceived Needs

	Not Religious (n=141)	**Moderately Religious (n=262)**	**Very Religious (n=40)**	**Total Sample (n=443)**
Factors Influencing End-of-Life Treatment Decisions[a] Mean (SD)				
A doctor must prolong life	**3.25 (1.2)***‡	**3.72 (1.2)**‡	**4.03 (1.2)***	3.60 (1.2)
A doctor must prevent suffering	**4.54 (0.8)***	**4.59 (0.7)**†	**4.23 (0.9)***†	4.51 (0.8)
The patient's religious beliefs	**3.01 (1.5)***	**3.25 (1.4)**†	**3.66 (1.4)***†	3.21 (1.5)
The doctor's religious beliefs	**1.51 (1.1)***‡	**2.24 (1.5)**†‡	**4.10 (1.2)***†	2.17 (1.5)
The current law	**3.82 (1.2)***	**3.85 (1.7)**†	**3.34 (1.2)***†	3.79 (1.2)
The policy on the ward	**3.26 (1.4)**	**3.39 (1.2)**†	**2.87 (1.2)**†	3.30 (1.3)
Economic considerations	1.76 (1.1)	2.06 (1.2)	1.68 (0.7)	1.93 (1.6)
The patient's wishes	4.33 (1.0)	4.26 (1.0)	4.18 (1.0)	4.27 (1.0)
The family's wishes	3.18 (1.2)	3.30 (1.2)	3.15 (1.1)	3.25 (1.2)
The patient's quality of life	4.14 (1.1)	4.10 (1.1)	3.89 (1.1)	4.09 (1.1)
Physician's Needs Concerning End-of-Life Care[a] **Mean (SD)**				
To have supportive group discussions to help in the treatment of dying patients	3.72 (1.1)	3.80 (1.1)	3.92 (0.77)	3.78 (1.0)
To receive clearer guidelines on the level of the hospital ward	3.30 (1.5)	3.45 (1.4)	3.25 (1.4)	3.39 (1.5)
To receive clearer guidelines on the level of the hospital	3.27 (1.5)	3.41 (1.5)	3.19 (1.4)	3.34 (1.5)
To receive clearer legal guidelines	**3.92 (1.4)**	**4.09 (1.3)**†	**3.46 (1.4)**†	3.98 (1.4)

SD = standard deviation

Values in **BOLD** are significantly different across the three groups at $p<0.05$.

*$p<0.05$ for comparison between Not Religious and Very Religious groups.

†$p<0.05$ for comparison between Moderately Religious and Very Religious groups.

‡$p<0.05$ for comparison between Not Religious and Moderately Religious groups.

[a] Responses on 5-point scale with a higher score indicating more agreement with the statement.

Many studies have shown that physician religiosity is related to attitudes toward end-of-life care. The same has been found for other health professionals (20–22). Religiosity has been strongly associated with physicians being less likely to report participating in euthanasia and physician-assisted suicide (1, 7, 9). These data are consistent with those findings. However, unlike euthanasia, which if it occurs at all, is a rare act stimulated (hopefully) by the will of the patient, withdrawing medical care is a common procedure that often occurs in the setting of patient decisional incapacity (23). Among patients dying in one U.S. hospital, 74% died only after a treatment was withdrawn (24). The decreased likelihood of the withdrawal of life-sustaining treatment reported by very religious physicians requires confirmation by review of clinical data. In addition, these differences might be explained by very religious physicians treating a preponderance of very religious patients. If that were the case, then the variation in withdrawing care might be a reflection of patient preferences. However, our data suggest that secular patients receiving care from very religious physicians might be at risk for less palliation and more aggressive care than they might want unless care were transferred to another physician.

The physicians included in this study are from a single culture. The religion of these physicians differs from that of most other physicians worldwide. However, the single-religion cohort permits the study of the relationship between religiosity and end-of-life care behaviors without the complexity of religious variation. Attitudes toward end-of-life care have been shown to vary across religious groups (25). The views expressed by the physicians in this study reflect Jewish law, which specifies the infinite value of human life (26) and the physician's imperative to heal (27). But the views must also be seen in the context of Israel, where in practice withholding care is acceptable, but withdrawing care is not yet clearly permissible (13, 28). No law in Israel clearly refers to these practices or to end-of-life care. Thus, the divergence between religious and non-religious physicians in withdrawing behavior may be larger than would be seen in societies that embrace care withdrawal. Conversely, these findings suggest that variation in physician practices by religiosity could have substantial implications for their Israeli patients.

These findings emphasize the importance of communication between physicians and patients about end-of-life care. Even for patients with chronic disease, such communication is not the rule (14, 29). We learn from these data that end-of-life communication should not be a one-way conversation. In addition to eliciting the patient's goals and preferences, the physician must express his or her views to the patient if these will affect care. Patients should know whether their physicians would be willing to withdraw care should the circumstances merit and whether their physicians would be willing to provide analgesia even if it meant cutting short life.

End-of-life communication was not strongly related to religiosity. If anything, more religious physicians agreed slightly more often with a patient's right to information and to participate in important care decisions. This finding is consistent with the more religious physicians' views on end-of-life care emanating from religious values rather than from a global paternalistic orientation. The factors described by physicians as influencing end-of-life treatment decisions are also consistent with religious values superimposed on medical decision making. Religious physicians were more likely to derive guidance in end-of-life decisions from religious views and somewhat less likely to rely on rules, but were no less likely to consider the views of patient and family.

The influence of religious views on withholding life-sustaining care from patients is evidenced by the striking comparison of intended life-sustaining care for the older man with metastatic cancer compared to what physicians would want for themselves in similar clinical circumstances. The very religious physicians held precisely the same views for the older man as they did for themselves, suggesting an underlying ethic that guides care. The less religious physicians wanted very different care for themselves than they would provide to the older man. Whether these responses suggest that non-religious physicians would more often rely on patients' preferences and thus are more flexible in their care decisions, and whether religious physicians would be less willing to withhold care if patients so desired requires study. The findings seem to indicate that very religious physicians have fewer dilemmas concerning end-of-life care, since they are guided by clear religious guidelines, while less religious and secular physicians face more internal conflict and perhaps more stress when treating terminally ill patients.

Conclusion

This study confirms that religiosity is an important factor in physicians' end-of-life views. The findings suggest that these views directly translate into end-of-life care behaviors that can have an impact on the way that their patients die. Revealing these perspectives is critical to providing end-of-life care that reflects patients' goals and preferences. These data demonstrate the need for careful evaluation of how religiosity and other physician beliefs shape the end-of-life care they provide. Further research into end-of-life practices in other cultures, such as in the religious diversity of the U.S., and across cultures, is needed in order to enhance our understanding of the effects of religiosity on end-of-life care. Better understanding of such influences may lead to development of interventions that will improve end-of-life care.

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Fibrous Pleural Tumor with Hypoglycemia:

Case Study

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Abstract

Many neoplastic tumors exhibit paraneoplastic syndromes manifested by endocrinopathy. This is particularly true of intrathoracic tumors such as lung cancers, thymomas, carcinoid tumors and mediastinal germ cell neoplasm. Fibrous tumors of the pleura are rare intrathoracic tumors, which are usually benign and often grow to huge size. A subset of these neoplasms present with the syndrome of hypoglycemia. Although first reported more than 70 years ago, the diagnosis is rarely considered when a patient presents with syncope and hypoglycemia. This article reports a patient who presented with a large pleural mass and a hypoglycemic syndrome. (The disease was surgically cured.) The probable mechanism of hypoglycemia is discussed.

Key Words: Pleura, tumor, hypoglycemia.

Case Report

A 62-YEAR-OLD WHITE MALE presented in 1996 with left-sided pleuritic chest pain, cough and fever. He had psoriasis and hypertension well controlled with nifedipine. He was an ex-smoker. Physical examination was normal except for dullness to percussion and decreased breath sounds over the left inferior hemithorax. Chest X-rays showed a left pleural effusion. Thoracentesis revealed an exudate of unknown etiology. A chest tube was inserted and intravenous antibiotics administered, with improvement. Subsequent chest CT scan revealed a left pleural mass. Closed biopsy of the pleura was negative for malignancy, revealing only nonspecific connective tissue. The patient refused thoracoscopy.

Two years later, in 1998, the patient experienced recurrent syncopal attacks, light-headedness and generalized weakness, usually upon awakening or about 5–6 hours after his last meal. Repeated tests of blood glucose level during these episodes revealed hypoglycemia. Blood glucose on one occasion was 32 mg/dL; it rose to 125 mg/dL with oral glucose administration. Physical examination revealed hypertension, psoriasis and dullness to percussion, with decreased breath sounds over the left hemithorax. Chest X-rays showed a huge pleural mass occupying the left lateral lower hemithorax (Fig. 1). Serum insulin level was low (4μU/mL) (normal fasting 5–20), insulin-like growth factor I (IGF-I) was 39 ng/mL (normal 152–494), IGF II was 661 ng/mL (normal 98–444). Thyroid function, liver function and serum cortisol were within normal limits.

A left thoracotomy was performed. A large lobulated mass, occupying the posterior and inferior portions of the entire left hemithorax, was encountered. There were dense adhesions to the parietal pleura. The left lower lobe and

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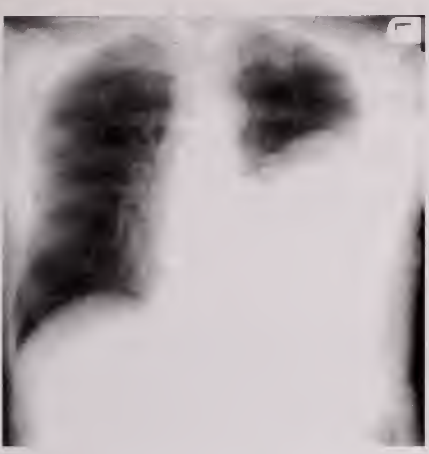

Fig. 1. Chest radiograph on admission to hospital showing a large pleural mass occupying the lower two-thirds of the left hemithorax.

the diaphragm were adherent to the mass. Multiple vessels entered the tumor (Fig. 2). Removal of the pleural mass required left lower lobectomy and diaphragm resection and repair. The resected mass measured 17×15×9 cm and weighed approximately 4 kilograms. Pathologic examination revealed a highly cellular spindle cell tumor, with rare mitoses. Many tumor cells were positive for CD34 immunoperoxidase stain. These findings were consistent with the diagnosis of solitary fibrous tumor (Fig. 3). The postoperative course was uncomplicated. In the seven years following surgery, there were no hypoglycemic symptoms and blood glucose was 90–100 mg/dL on several occasions. Immediate post-resection IGF-I was 191 ng/mL and IGF-II was 515 ng/mL. Subsequent IGF-I and IGF-II levels were normal: 114 ng/mL and 355 ng/mL, respectively.

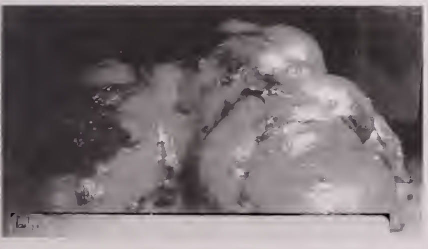

Fig. 2. Photograph of the resected huge pleural fibroma measuring 17×15×9 cm and weighing approximately 4 kilograms.

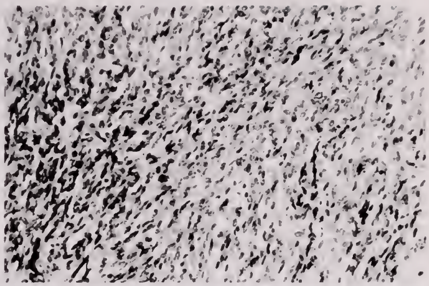

Fig. 3. Microscopy of resected pleural tumor demonstrating high cellularity, spindle cells and few mitotic figures, which showed positive staining with CD34. Consistent with a solitary fibrous tumor of the pleura. (H+E, 50x original magnification).

Discussion

Solitary fibrous tumors (SFT) are spindle cell neoplasms. They are usually benign, but may be malignant. Klemperer and Rabin described benign fibrous tumors of the pleura (1). Most authors believe they arise from submesothelial connective tissue (2, 3). In the thorax, they usually involve the pleura, but can be intrapulmonary or mediastinal. Histologically, they show a variety of arrangements, from a "patternless pattern" to a hemangiopericytoma-like or diffuse sclerosing appearance, and stain positive for CD34 and vimentin (4). Smooth muscle tumors and malignant peripheral nerve sheath tumors show occasional positivity with this antibody, but these spindle cell tumors usually can be identified with an immunohistochemical panel using specific markers such as actin, desmin and S-100 (5).

Most solitary fibrous pleural tumors cause minimal symptoms despite growth to huge proportions. When present, the most common symptoms are cough, chest pain, dyspnea and pulmonary osteoarthropathy. Hypoglycemia is rare (6, 7). Malignant pleural tumors may metastasize. Most neoplasms associated with hypoglycemia are pancreatic β-cell tumors. Doege reported the first patient with an intrathoracic fibrous tumor associated with hypoglycemia in 1930 (8). In 1981, Briselli et al. reviewed 360 cases of soltary pleural fibrous tumors reported since 1942. Four percent had symptomatic hypoglycemia (9); one instance of hypoglycemic coma was fatal (10).

Several mechanisms for hypoglycemia associated with solitary fibrous tumors have been proposed (11 – 13); these include secretion of insulin-like growth factor II (IGF-II or big IGF-II), increased utilization of glucose by the huge tumor, insulin receptor proliferation mediated by the solitary fibrous tumor, decreased gluconeogenesis, and decrease in effective glucagon secretion.

Secretion of IGF by the tumor is the most widely accepted mechanism for hypoglycemia in fibrous masses (14 – 16). Stuart et al. reported an increased number of insulin receptors in these large tumors (17). The finding of increased IGF-II with hypoglycemia before resection and decreased IGF-II with abatement of hypoglycemia after resection, as in our patient and a similar patient reported by Filosso et al. (18), supports this hypothesis. Further evidence in favor of tumor production of IGF is the high concentration of messenger RNA for IGF-II in an excised mesenchymal tumor reported by Daughady et al. (19).

Our patient had hypoinsulinemic hypoglycemia and suppressed serum pituitary growth hormone and IGF I levels, and a high concentration of IGF II. After resection the concentrations returned to normal. Baxter et al. suggested that there is an overexpression of IGF II, which is responsible for hypoglycemia in solitary fibrous tumors (20). IGF I and IGF II are arranged in a ternary complex with IGF binding protein. Failure to form a ternary complex is thought to explain the enhanced hypoglycemic activity of circulating IGF-II in these patients. This failure to form a ternary complex may occur because these complexes are pituitary-growth-hormone dependent and most of these patients have a subnormal level of pituitary growth hormone (16, 21).

Conclusion

When confronted with a patient with hypoglycemia and suppressed insulin levels, non-islet cell hypoglycemia should be considered. The case reported here demonstrated that a solitary fibrous pleural tumor should be considered in the differential diagnosis. Hypoglycemia due to an imbalance of circulating IGF I and IGF II caused by the tumor may be the primary clinical feature of these patients. Surgical resection of the tumor is curative. Rarely, the pleural tumor is malignant and recurs locally or at a metastatic site.

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Cytomegalovirus Colitis in an Immunocompetent Patient with Amebiasis:

Case Report and Review of the Literature

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Abstract

Most cases of cytomegalovirus colitis occur in adults with severe immune deficiency. Only a few cases involving immunocompetent patients have been reported. We describe the first case reported in English, of cytomegalovirus colitis in an immunocompetent patient with preceding amebiasis. Eight previous cases have been reported of cytomegalovirus colitis occurring after colonic mucosal injury in immunocompetent patients. Similar to our case, all eight of these cases resolved without the use of antiviral therapy. This suggests that disruption of colonic mucosa may predispose immunocompetent patients to cytomegalovirus colitis, and that the colitis may become self-limited once the preceding intestinal damage resolves.

Key Words: Cytomegalovirus, colitis, amebiasis, immunocompetent.

Introduction

CYTOMEGALOVIRUS (CMV) is a common human viral infection, occurring in 40 – 100% of the adult population (1). Most primary CMV infections are asymptomatic (2). However, CMV can cause a variety of illnesses, including gastrointestinal illness. The colon is one of the organs most commonly involved. CMV usually affects immunocompromised subjects, including patients taking immunosuppressant medications and those with acquired immune deficiency syndrome (AIDS), organ transplants, or cancer (3). It has rarely been reported in immunocompetent subjects (4 – 17). Many of these cases were preceded by some form of mucosal injury (7 – 12). This report describes the first case reported in English, of CMV colitis in an immunocompetent patient with preceding amebiasis. It then discusses CMV colitis in the immunocompetent host, with speculation on the importance of preceding colonic mucosal injury.

Case Report

A 29-year-old, previously healthy white male noted diarrhea two weeks after a four-day vacation in Cozumel, Mexico. He reported that he had up to six watery, non-bloody bowel movements per day, which became bloody after two days. He also had fevers to 38.9°C, fatigue, chills, "sweats," and anorexia, with three kilograms of weight loss. He denied any abdominal pain, nausea, vomiting or jaundice. The patient was evaluated by his primary care physician, who prescribed oral levofloxacin 500 mg once per day for presumed traveler's diarrhea. The patient had persistent fevers and bloody diarrhea after four days on levofloxacin and was subsequently admitted to the hospital.

The patient reported that in Mexico he had consumed fresh fruits, vegetables, dairy products, and local tap water. He denied any previous travel outside the United States. The patient had no significant medical history, and specifically no previous sexually transmitted diseases or parasitic infections. He had taken no medication other than levofloxacin. He did report occasional alcohol intake and a history of promis-

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The work was performed at the Department of Internal Medicine, Wright-Patterson Medical Center, Wright-Patterson Air Force Base, OH, and presented at the American College of Gastroenterology National Fellows' Forum in Vail, Colorado, June 22, 2002. It was updated as of January 2004.

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cuous, unprotected sexual activity. The patient denied any intravenous drug abuse, tattoos, tobacco use, or sex with men.

Initial examination was notable for a temperature of 37.7°C, pulse of 113 beats/min, respiratory rate of 20/min, and blood pressure of 135/82 mm Hg. He appeared well developed, well nourished, and in no apparent distress. Head and neck examination revealed oropharyngeal erythema without exudate, sub-centimeter, scattered cervical adenopathy, and no scleral icterus. His abdomen was soft and nontender without organomegaly. Rectal examination was normal and without any bright red blood or melena.

Admission laboratory studies were significant for alanine aminotransferase of 224 U/L (normal, 24 – 63 U/L) and aspartate aminotransferase of 143 U/L (normal, 12 – 37 U/L). Lactate dehydrogenase was 423 U/L (normal, 100 – 190 U/L). White blood cell count was $7.9 \times 10^3/\text{mm}^3$, with a differential count of 42% neutrophils, 45% lymphocytes (with many atypical lymphocytes), and 13% monocytes. Serum electrolytes, hemoglobin, hematocrit, total bilirubin, and alkaline phosphatase were all normal.

CMV IgG and IgM antibody titers were obtained because there was a clinical suspicion of CMV, since the patient had pharyngitis, cervical adenopathy, elevated aminotransferases and atypical lymphocytes. CMV IgM antibody was positive at 9.84 index (<0.9 is negative), while CMV IgG antibody was negative at 1.23 AU/mL (<15 AU/mL is negative). Serologies also showed an elevated *Entamoeba histolytica* titer of 70 AU/mL (>50 AU/mL is indicative of current or recent invasive amebiasis as per Epidemiology Division, Brooks Air Force Base, TX) (18). Human immunodeficiency virus (HIV) serology, HIV RNA by polymerase chain reaction, blood cultures, monospot test, hepatitis A IgM, hepatitis B surface antigen and core IgM, hepatitis C antibody, and malaria smears were all negative. Stool studies during the patient's hospitalization were positive for occult blood, and negative for *Clostridium difficile*, ova and parasites (including *Cryptosporidium*), fecal leukocytes and enteric bacterial pathogens.

Chest and abdominal x-rays were within normal limits. Right upper quadrant ultrasonography did not reveal any focal mass lesions or abscess formation. Contrast-enhanced abdominal computed tomography revealed splenic enlargement with a craniocaudal span of 15 cm, and a normal liver without evidence of abscess formation.

Colonoscopy was performed on the third hospital day. The distal sigmoid colon had mild, patchy inflammation. In the proximal descending colon and at the splenic flexure, there was severe inflammation with bowel wall edema and multiple shallow, serpiginous ulcerations. The colonoscope was not advanced beyond the splenic flexure because of the risk of perforation, given the severe inflammation. On biopsy, a moderately dense inflammatory cell infiltrate was present in the lamina propria of the colonic mucosa. Neutrophils were seen in clusters around blood vessels with dilated endothelial cells. Some cells had intranuclear basophilic inclusions set off from the nuclear membrane by a clear halo, consistent with CMV. These findings were confirmed with immunohistochemical studies, which showed a significant number of immunoreactive CMV cells in the stroma.

The patient was treated for amebic colitis with oral metronidazole 750 mg three times per day for ten days, along with oral paromomycin 1000 mg three times per day for seven days. His symptoms completely resolved over a three-week period without the administration of any antiviral agents. The patient has remained healthy without recurrent symptoms during 16 months of follow-up.

Discussion

CMV colitis usually affects immunosuppressed patients, including those having organ transplantation, hematological malignancies, or AIDS. It is uncommon in immunocompetent subjects (4 – 17). The most common presenting manifestations of CMV colitis in immunocompetent patients are diarrhea, fever, gastrointestinal bleeding and abdominal pain (14 – 16). Endoscopy most often shows erosive colitis with multiple ulcers (14, 16). Complications include massive hemorrhage, toxic megacolon, perforation, and protracted inflammatory bowel disease (14). In immunosuppressed patients, CMV colitis almost always occurs secondary to reactivation of latent CMV infection. However, in the immunocompetent patient, it often accompanies primary CMV infection (14).

It is unclear why some immunocompetent individuals develop CMV colitis. One possibility is that disruption of the colonic mucosa can predispose patients to colonic CMV disease (8, 11, 12). Vogel demonstrated *in vivo* and *in vitro* that CMV has a propensity to infect proliferating endothelial cells in inflamed, damaged tissue (19). Levine and co-workers initially described CMV colitis as a superinfection of another intestinal disorder (20). In a study by Hinnant and colleagues, 79% of AIDS patients with CMV colitis had coexistent gastrointestinal infections (21). It is not known how preceding colonic injury may predispose patients to CMV colitis. One possibility is that the presence of colonic mucosal injury and inflammation may promote migration of CMV-infected macrophages to the colon.

Of the small number of CMV colitis cases with immunocompetent hosts, eight occurred after a preceding local colonic insult (Table) (7–12). Two cases occurred after *Shigella* dysentery (7, 8). Three cases of CMV colitis occurred less than one week after traumatic receptive anal intercourse (9, 10). Two cases presented less than two weeks after mucosal damage caused by ischemia (7, 11). One case occurred in an infant who had enterocolitis from bovine milk allergy (12). CMV colitis was confirmed by endoscopic biopsy in all cases. None of the patients had any evidence of immunodeficiency at the time of symptoms or during follow-up.

Our patient was judged to be immunocompetent from his negative tests for HIV antibody and HIV RNA, his normal leukocyte count, and the absence of prior infections or illnesses in his medical history. He probably became predisposed to develop CMV colitis secondary to the damage caused by the colonic amebiasis that he contracted while he was in Mexico. Although the stool studies and the colonic biopsies did not show evidence of amebic cysts or trophozoites, organisms may have been excreted in an acyclic manner and may have been unevenly distributed in the colon, causing falsely negative samples (22). Approximately 5–15% of amebiasis may be missed despite examination of three stool specimens (22), and the detection rate of trophozoites by histopathologic examination of colonic biopsy specimens is highly variable (23). Misdiagnosis may be even higher in laboratories that are not accustomed to detecting amebic trophozoites (24).

The diagnosis of amebiasis in our patient is based on the clinical history, the response to anti-amebic therapy, and the positive serology. The positive serology is specific for recent amebiasis infection in this patient, because he had never previously traveled to an endemic region. Moreover, he did not have any risk factors for previous amebiasis exposure, such as homosexuality, recent immigration, or residence in a chronic psychiatric care facility.

Our case is similar to the previous cases in terms of patient presentation, treatment and out-

TABLE

Summary of Reported Cases of CMV Colitis in Immunocompetent Patients with Preceding Colonic Injury

Case (reference)	Age, years /Sex	Preceding Insult	Symptoms	Treatment	Outcome
1 (7)	71/female	*Shigella* dysentery	Bloody diarrhea, fever, constipation	Supportive	Resolution in 3 weeks
2 (8)	62/female	*Shigella* dysentery	Bloody diarrhea	ofloxacin	Resolution in 4 weeks
3 (9)	37/female	Anal intercourse	Hematochezia, rectal pain	Antibiotics	Resolution in 2 weeks
4 (9)	25/male	Anal intercourse	Constipation, hematochezia, fever, headache	Antibiotics	Resolution in 4 weeks
5 (10)	38/female	Anal intercourse	Constipation, fever, anorexia, rectal bleeding, rectal pain, tenesmus	Supportive	Resolution in 2 weeks
6 (7)	59/female	Cardiogenic shock	Bloody diarrhea	Supportive	Resolution in 20 days
7 (11)	72/female	Perioperative hypotension	Bloody diarrhea, fever	salazopyrine, metronidazole	Resolution in 4 weeks
8 (12)	<1/male	Allergic colitis	Rectal bleeding	Supportive	Resolution
9 (current case)	29/male	Amebiasis	Bloody diarrhea, anorexia, fever	metronidazole, paromomycin	Resolution in 3 weeks

come. Each of the patients had preceding disruption of the colonic mucosa prior to the development of CMV colitis. None of the patients received specific antiviral therapy for CMV colitis. The main treatments these patients received were supportive measures, along with treatment of the underlying cause of the initial colonic insult. All nine cases of CMV colitis resolved without major complications. It appears that CMV colitis becomes self-limited as the initial colonic injury resolves.

In contrast to patients with preceding injury of the colonic mucosa, those immunocompetent patients without a previous insult may not have a favorable prognosis. In one review, only 3 of 15 patients without previous colonic insults had self-limited disease (14). Five patients required either partial or total colectomy, and four patients died. Perhaps patients without prior mucosal injury have an unappreciated mild immunodeficiency, or they require a higher viral exposure, which lead to more severe systemic disease.

With regard to treatment, the role of antiviral agents or surgery for CMV colitis in immunocompetent patients is not clear. In a comprehensive review of CMV colitis in immunocompetent patients (15), the overall mortality rate was 32% (13/38). Mortality was 25% (5/20) in patients who received supportive therapy alone, 25% (2/8) in patients who received antiviral therapy alone, 40% (2/5) in patients who had surgery and antiviral therapy, and 80% (4/5) in patients who had surgery alone (15). In light of the high morbidity and mortality documented in previous reviews, several authors have recommended antiviral agents for the treatment of CMV colitis in immunocompetent patients (14, 15). Based on the favorable outcome of the patient described in our report, we feel that specific antiviral agents are not always necessary in the treatment of CMV colitis in immunocompetent patients who have a preceding colonic insult that is treatable or self-limited.

This case adds to a small body of literature on CMV colitis in immunocompetent patients. Based on this limited experience, we feel that preceding disruption of the colonic mucosa probably represents a risk factor for CMV colitis in immunocompetent patients. When a preceding, reversible colonic insult is present in these patients, specific antiviral agents to treat the CMV colitis may not be necessary.

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Liver Abscess in Crohn's Disease:

A Report of Three Cases

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Abstract

Liver abscess is a rare complication of Crohn's disease and must be considered part of the differential diagnosis. We present three case reports and a review of the literature.

The incidence of liver abscess is higher in patients with Crohn's disease than in the general population. Since Crohn's disease patients who present with a liver abscess generally do not respond to medical management alone, surgical or percutaneous drainage of the abscess is necessary.

Key Words: Crohn's disease, liver abscess, abscess drainage, complications, surgery, inflammatory bowel disease.

Introduction

Liver abscess is a rare complication of Crohn's disease (CD), as evidenced by a paucity of cases in the literature (1, 2). In 1870, Fagge described hepatic abscesses in a patient with ulceration of the colon (3, 4); it was probably due to Crohn's colitis, since there have been no documented cases of liver abscess associated with ulcerative colitis. The first cases of liver abscess complicating CD were documented in the 1940s. The incidence of liver abscess in patients with CD is 8 – 16 per 100,000, about 10 – 15 times that found in the general population, even though intra-abdominal abscesses are encountered relatively often in CD (3). Diagnosis of the abscess is often delayed because its clinical presentation can be similar to an exacerbation of CD or may precede the diagnosis of CD. Liver abscesses usually appear as late sequelae of CD. There are only six reports of liver abscesses which developed prior to the establishment of the diagnosis of CD (5 – 7). And to our knowledge, aseptic abscesses have been reported only once (8). We report three cases of liver abscesses associated with CD; the first involves an aseptic liver abscess that led to the diagnosis of CD, and the others involve two patients with CD and the subsequent identification of liver abscess.

Cases Reports

Case 1

A 52-year-old man was hospitalized with a two-week history of fever, chills, and right upper quadrant abdominal pain. There was no history of diarrhea or intermittent episodes of cramping abdominal pain. A colonoscopy performed one year previously had been normal. The patient's sister had quiescent CD. On physical examination, the patient had a temperature of 39.5° C and significant right upper quadrant tenderness. Laboratory data included a white blood cell count of 20,800 cells/mm^3 (< 10,000 cell/mm^3), platelet count of 1.2 million/mm^3 (100,000 – 400,000 cells/mm^3), Alanine aminotransferase (ALT) 8 U/L (1 – 53 U/L) and total bilirubin of 0.5 mg/dL (0.1 – 1.2 mg/dL). Ultrasound examination revealed several hypoechoic nodular lesions in the right hepatic lobe. Abdominal CT demonstrated multiple hypodense lesions suggestive of liver abscesses. Ultrasonographic percutaneous biopsy of one of the lesions yielded purulent

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material. Culture of the fluid did not grow any organisms. Blood cultures were normal. A small bowel series revealed dilated loops of small bowel, as well as two strictures suggestive of CD. Asacol 800 mg BID and IV Unasyn 1.0 gm q6h were begun. Twenty-four hours later the patient underwent an ileo-colic resection and drainage of two liver abscesses. Operative findings during the procedure included purulent liver abscesses, two ileo-ileal fistulas, inflammation and narrowing of the terminal ileum. The postoperative course was uneventful, and the patient was discharged home on postoperative day #8. The pathology report revealed active Crohn's ileitis with ulcerations, sinus tracts, transmural chronic inflammation and mesenteric fibrosis.

Case 2

A 23-year-old man with a one-year history of CD was admitted with a three-week history of fevers, chills, nausea, and right upper quadrant abdominal pain. On physical examination, the patient had a temperature of 39.5° C, scleral icterus, and right upper quadrant tenderness. Laboratory tests included a white blood cell count of 31,000 cells/mm^3, total bilirubin of 2 mg/dL, alkaline phosphatase of 193 U/L (30 – 110 U/L), and ALT 72 U/L. A small bowel series demonstrated multiple entero-enteric and colo-enteric fistulae consistent with CD of the terminal ileum. IV hydrocortisone 50 mg q8h, IV ciprofloxacin 400 mg BID and metronidazole 500 mg BID, was initiated. A CT scan of the abdomen and pelvis demonstrated a 10 cm septated abscess in the dome of the right lobe of the liver, and a 3 cm psoas abscess adjacent to the inflamed terminal ileum. CT-guided percutaneous drainage of the liver abscess yielded 320 cc of purulent material. Cultures grew *Streptococcus viridans*. The antibiotics were changed to IV Zosyn 3.375 mg q6h. The psoas abscess could not be drained percutaneously. At laparotomy, an inflammatory mass containing purulent and necrotic material was noted in the liver and in the psoas muscle. The abscesses were drained, and ileo-colic resection was performed. Follow-up CT on postoperative day twelve demonstrated a residual hepatic abscess, which was drained using CT guidance. A pigtail drain was left in place for three weeks. The patient was treated with IV Zosyn 3.375 g q6h for 10 days and discharged home with PO augmentin 875 mg BID for 5 days.

Case 3

A 56-year-old man was admitted with a ten-day history of non-productive cough, fever, anorexia and lethargy. There was no history of abdominal pain, diarrhea, nausea or vomiting.

The patient had a medical history of Crohn's disease for 30 years, without medical treatment for the previous 10 years. Twenty-five years prior to admission, the patient had undergone incision and drainage of perirectal abscess. Colonoscopy performed two years prior to admission was normal.

On physical examination, the patient had a temperature of 39° C, heart rate of 105 and blood pressure of 110/70 mmHg. The chest was clear to auscultation, the abdomen was soft, non-distended with mild tenderness in the right upper quadrant, without peritoneal signs. Laboratory data included a white blood cell count of 17,300 cells/mm^3, total bilirubin 2.1 mg/dL, direct bilirubin 1.5 mg/dL (0.0 – 0.8 mg/dL), alkaline phosphatase 208 U/L and ALT 30 U/L.

Abdominal CT (Fig. 1) demonstrated a hypodense liver lesion suggestive of abscess and an entero-enteric fistula involving the sigmoid colon and cecum. The patient was treated with IV cefepime 1 g BID and IV metronidazole 500 mg q8h. The next day the patient underwent CT-guided drainage of the abscess (Fig. 2). Gram stain revealed gram positive cocci, and antibiotics were switched to IV Unasyn 1.0 mg q6h. Two days later, the temperature went down to normal and the white cell count was 10,000 cells/mm^3.

On hospitalization day (HD) #4, the patient underwent a small bowel series (Fig. 3), which showed strictures in the terminal ileum as well as an ileo-cecal fistula and an ileo-sigmoid fis-

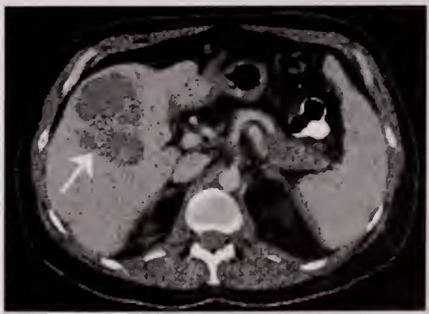

Fig 1. CT scan showing multiloculated liver abscess.

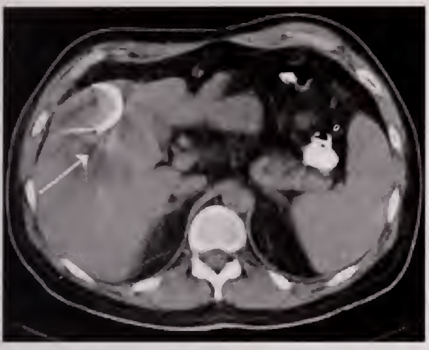

Fig 2. CT scan showing percutaneous drainage of the abscess.

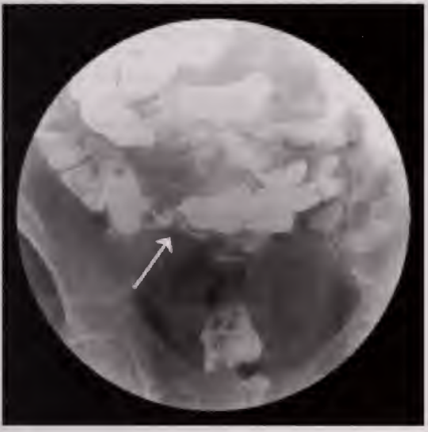

Fig 3. Small bowel series showing ileo-sigmoid fistula.

tula. Colonoscopy showed inflammatory changes in the terminal ileum, evidence of a fistula involving the cecum, collection of pseudopolyps at 30 cm and at 15 cm, from the anal verge, consistent with fistulization to these areas. The distal 10 cm demonstrated inflammatory changes consistent with Crohn's scar tissue. On HD #8, the patient underwent ileo-colic resection, takedown of ileo-sigmoid fistula, anterior resection and drainage of residual liver abscess. The postoperative course was uneventful; the patient was treated with IV Unasyn for 7 days and discharged home on postoperative day #9 in good condition.

Discussion

Liver abscess is a rare complication of CD. Mir-Madjlessi calculated the incidence to be 114–297 per 100,00 cases of CD vs. 8–16 per 100,000 in the general population (1). All of the case series and case reports, including the present report, support a male predominance with a male: female ratio of 23:8 (1–8). This is in contrast to the equal male-to-female ratio found in CD in general. The average age of the patients reported in the literature ranged from 24–44 years (1, 2, 7). While most of the abscesses developed in patients with longstanding CD, six occurred in patients in whom the initial presentation of CD was the liver abscess (3, 5). The mean duration of CD prior to the development of liver abscess ranged from 6 months to 9 years (1, 2, 5). Our patients described as Case 2 and Case 3 had CD for one year and 30 years, respectively, while the patient described as Case 1 presented with a liver abscess prior to the diagnosis of CD.

Several factors have been implicated as possibly predisposing to, or being associated with, development of liver abscess. Steroids and antibiotics have been suggested as a possibility, but there is insufficient evidence to support this (1, 3). Considering the widespread use of antibiotics among CD patients, it would seem that the prevalence of liver abscess should be higher if this were truly a predisposing factor. There is no significant association with any specific location of intestinal disease activity. In most of the reported cases (3, 5, 8), the patients did have inflammatory or perforating disease as opposed to fibrostenotic disease. Again, considering the number of patients with CD who develop fistulae and intra-abdominal abscesses, one might expect the incidence of liver abscess to be higher if this were truly a predisposing factor. In two reported patients, the CD was quiescent at the time of the development of the liver abscess (5). In all of our cases, active CD of the ileum was present. The presence of fistulous disease and intra-abdominal abscesses has been suggested by some to be a predisposing factor (1, 2). Our patient, Case 1, had fibrostenotic disease, while the others had fistulizing disease. Several mechanisms have been proposed regarding the development of a liver abscess. These include direct extension of an intra-abdominal abscess into the liver via the portal vein from intra-abdominal infection, indirectly from complications of CD (i.e., biliary disease), and from sepsis occurring in a carcinoma which had metastasized to the liver (1).

The clinical picture with which these patients present is also quite variable. Certain characteristics are commonly found, such as fever, elevated white blood cell count and elevated alkaline phosphatase. In only a few patients were the other liver enzymes elevated, as was seen in Case 2. Intestinal symptoms may not always be present. Tenderness, fullness and palpable mass in the right upper quadrant may not be appreciated. In short, there is often no clear evidence on clinical presentation to suggest the presence of liver abscess.

However, the advent of advanced imaging techniques, such as CT scanning and ultrasound, has facilitated diagnosing this rare complication. Early diagnosis has improved survival rates. In the 12 documented cases during the past 10 years, there has been only one death, an 87-year-old patient who experienced an acute myocardial infarction (3, 5). This is in comparison to the 19 previous cases, in which there were 7 mortalities, presumably related to inability to correctly identify liver abscess as the underlying problem (1, 2, 4, 6–8).

Because of the infrequency of this serious complication in clinical practice, controversy still exists as to which treatment modality is appropriate. Attempts have been made to treat liver abscesses with antibiotics alone; the results have been dismal. Greenstein reported a 75% mortality rate in the group of patients treated with antibiotics alone (3). Most of the patients had some form of percutaneous drainage performed, usually in conjunction with insertion of a pigtail catheter for continued drainage. There does not appear to be any consensus as to type and duration of antibiotics. The duration of intravenous antibiotics ranged from 2–6 weeks. Oral antibiotics were also utilized. One patient received oral penicillin for 3 months after surgical drainage of his abscesses and intravenous penicillin as well (7). Another patient underwent ultrasound guided percutaneous drainage of his liver abscess and then received a 6-week course of oral amoxicillin, having never received intravenous antibiotics at all. The choice of antibiotics is dependent on the organisms obtained at culture. In Case 2, the culture of the liver abscess revealed *S. viridans*. There is clear evidence that Streptococcus species, particularly *S. milleri*, are especially likely to be cultured from a CD-related abscess. This organism is identified repeatedly throughout the cases reviewed, as in Case 3 (1, 2, 5–7).

Development of disseminated sterile abscesses preceding inflammatory bowel disease, as seen in Case 1, is a rare presentation. Negative bacterial tests and serologies do not necessarily mean that the abscess is aseptic: slowly growing organisms and previous antibiotic therapy could explain the absence of causative agents, and other systemic disease could predispose the patient to abscess formation. In Case 1, CD was the only systemic disease that could be linked to the abscess.

Regarding percutaneous vs. surgical drainage, many patients were managed satisfactorily with percutaneous drainage and antibiotics (1, 2, 5, 8). Those patients in whom percutaneous drainage was unsuccessful (i.e., multiple abscesses which were not connected) required surgery, especially if there was other intra-abdominal pathology that also had to be addressed. Under these circumstances, the majority of authors (1–3, 5–7) advocate surgical drainage.

Summary

Liver abscess is a rare complication of patients with CD. Despite advances in imaging, the diagnosis is frequently delayed and a high degree of suspicion is required. In our opinion, shaking chills and fevers with elevated white cell count and alkaline phosphatase should arouse suspicion. Abdominal CT scan or ultrasound should be performed in order to make an earlier diagnosis.

Broad spectrum IV antibiotics combined with percutaneous or surgical drainage is the treatment of choice.

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“Thou Shalt Not Kill”:

Some Legal and Linguistic Problems

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Abstract

Large plaques of the religious precepts generally known as the Ten Commandments were recently placed in official public spaces in several states. This practice has been successfully challenged in federal courts of appeals, and the challenge was upheld by the Supreme Court in April 2003. Yet there is another problem with such plaques, if older translations are used. “Thou shalt not kill” is actually a mistranslation of the Hebrew, “You shall not murder.” The two statements are not synonymous, yet many people in the world still use archaic biblical translations, with unfortunate bioethical consequences. There is also widespread usage of a non-commandment, “Thou shalt not kill; but needst not strive officiously to keep alive.” This is not a biblical injunction; it is a line from A.H. Clough’s satirical poem, ”The Latest Decalogue.”

Key Words: Religion, bioethics, murder.

SOME SOUTHERN STATES have recently placed plaques of the Ten Commandments in official public spaces. Thus, in August 2001, Roy Moore, the newly elected state supreme court chief justice of Alabama, placed a granite Ten Commandments monument weighing 5,280 pounds in the rotunda of the state judicial building (1). And recently, a large monument bearing the Ten Commandments was displayed on the state capital grounds in Frankfort, Kentucky (2). Both monuments contain the words “Thou shalt not kill.”

The situation presents both legal and linguistic problems.

The American Constitution

Placement of these monuments has been challenged by lawsuits based on the principle of separation of church and state in the establishment clause of the First Amendment of the American Constitution. In October 2002, the US Court of Appeals for the Sixth Circuit in Cincinnati held that the size and placement of the monument conveyed official endorsement of a religious message and ruled against its placement (2). This ruling was confirmed in November 2002 by the Federal District Court in Montgomery, Alabama (3). Ten states appealed to the US Supreme Court to review these rulings, but on April 29, 2003, the Court refused to hear the appeals because of the unanimity of the lower courts’ decisions (4), and again refused on August 20, 2003 (5). State Supreme Court Justice Moore was therefore suspended from the bench on August 22 (6) and the monument was removed from public view on August 27 (7). Roy Moore was ousted as chief justice for refusing to comply with the Court’s ruling on November 13 (8).

The Ten Commandments and Their Mistranslation

In addition to the constitutional problem with these plaques, there is a linguistic one. Namely, they contain a mistranslation of the original Hebrew. The statement in Exodus

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20:13 and its repetition in Deuteronomy 5:17, according to the original Hebrew, means "You shall not murder," which is the clear and unequivocal English meaning of the Hebrew *Lo tirtsach*.

Unfortunately, St. Jerome (342–420 CE), in his Latin Vulgate, used the phrase *Non occides*, "you shall not kill." The German equivalent was chosen by Luther *(Du sollst nicht töten)*, and the English equivalent was selected by King James' translation committee for their great Authorized Version of 1611. "Thou shalt not kill" thus remained virtually the only wording of the command in English until the 20th century brought with it new, more accurate translations. Some of the new translations have provided the correct English translation for the original Hebrew term in the command. This correction helps clarify the parallel between the Old Testament legal system and modern legal systems on the issue of murder. Most modern legal systems distinguish between the justified "kill" and the wrongful "murder."

Nevertheless, the statement is still quoted as "Thou shalt not kill" by many English-speaking Christians, including a recent Archbishop of York (9) and an editor of *The Times* (10), brought up as they probably were with the Authorized Version (11). "Thou shalt not kill" is also used by some religious fundamentalists as an argument for pacifism and against, for example, conscription into the armed forces and judicial capital punishment. From the medical and bioethical standpoints, "Thou shalt not kill" has been used to oppose certain interventions by physicians at the beginning and end of life. Yet here too the distinction between killing and murder can be crucial. Health care providers who actively hasten the death of their terminally ill patients are widely believed to have committed murder. But in some states, doctors who (at the request of authorized surrogates) withdraw life-support treatment, leading to certain death of their patients in brain-dead vegetative states, would be considered to have performed a "mercy killing" that could be legally justified.

Another Commandment?

Occasionally, one hears a supposed variation of this commandment: "Thou shalt not kill; but needst not strive officiously to keep alive." This is sometimes cited as proverbial wisdom for a "non-interventionist" policy of medically hastening death without suffering. This policy is followed today by many physicians, regardless of their repeatedly being told by bioethicists and philosophers that there is no ethical difference between such a "passive" policy and active, direct killing of the patient, or physician-assisted suicide (12), and even when they are aware of its irony (13).

This injunction is not from the Bible at all. It is whimsy from Oriel College, Oxford, by one of its fellows. It was written by the 19th century poet Arthur Hugh Clough. At Oxford University, in the agnostic swirl of Bentham's utilitarianism, Clough lost his faith and (as a result) his fellowship. In his spiritual anguish (around 1842) he wrote (and then concealed) a satirical poem, "The Latest Decalogue," which was not published until after his death in 1861 (14):

> Thou shall have one God only; who
> Would be at the expense of two?
> No graven images may be
> Worshipped, except the currency:
> Swear not at all; for for thy curse
> Thine enemy is none the worse:
> At church on Sunday to attend
> Will serve to keep the world thy friend:
> Honour thy parents; that is, all
> From whom advancement may befall:
> Thou shalt not kill, but needst not strive
> Officiously to keep alive:
> Do not adultery commit;
> Advantage rarely comes of it:
> Thou shalt not steal; an empty feat,
> When it's so lucrative to cheat:
> Bear not false witness; let the lie
> Have time on its own wings to fly:
> Thou shalt not covet; but tradition
> Approves all forms of competition.
>
> The sum of all is, thou shalt love,
> If anybody, God above;
> At any rate shall never labour
> *More* than thyself to love thy neighbour.

Just as Galsworthy meant his *Forsyte Saga* as bitter social satire, only for it to become a wallow in Edwardian nostalgia, so it has been Clough's posthumous fate for the bitter irony of his "Decalogue" to be lost, so that it is cited instead as a sacred commandment of bioethical sophistry.

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Letter to the Editor

Eighty Hours a Week:

A Third-Year Resident's Perspective on Duty-Hour Limitations

NOT SINCE WATCHO AND OSKI'S ARTICLE entitled "Bilirubin 20 mg/dL = Vigintiphobia" have directors of pediatric training programs been so obsessed with absolute numbers (1). Concerned about issues of sleep deprivation among housestaff and their implications for care, the Accreditation Council for Graduate Medical Education (ACGME) decided to impose national mandatory limits on how many hours residents may spend in the hospital. The new regulations limit on-duty hours to 80/week, with no more than 24 consecutive hours of on-site duty, assurance of a 10-hour grace period between clinical activities, and an average of one day per week free of hospital responsibilities (2).

This policy has produced a dramatic restructuring of clinical rotations in most pediatric residency training programs, as program directors seek innovative strategies to adhere to these rules while maintaining adequate physician staffing. Furthermore, the changes have sparked vigorous debate regarding the new philosophy of resident-physician training and its implications for patient care. The debate is similar to discussions that took place in 1989, in response to New York State Code 405, upon which the new national guidelines are based. While it is believed that the rules will "greatly enhance medical education" and continue to produce "the highest quality physician," there remains concern that the system will erode the doctor-patient relationship and compromise the qualities of professionalism which distinguish medicine from other careers (3, 4).

What has been missing from this debate is a review of the issues by a pediatric house officer who has experienced both training systems. With two years in a classically designed q4 call system, which consists of 36 hours of consecutive duty every fourth night for inpatient services and 72–108 duty-hours per week, and a final year in a program tailored to meet the ACGME criteria, I may offer a helpful perspective on how the requirements translate into pediatric-specific training. As the ACGME's own *Annotated Bibliography of Selected Articles on Resident and Physician Duty* hours includes only one article devoted to pediatric residents, it is important to evaluate the new rules in the context of some unique aspects of our medical specialty (5).

One of the greatest assets of pediatric residency is the opportunity for the physician to uninterruptedly observe the course of a disease requiring hospitalization. If the major goal of residency training is to provide an ideal environment for learning pediatrics, then hands-on teaching and didactic sessions are critical to our development (4). The ACGME guidelines, in providing for a six-hour window in order to transfer care and attend conferences, have made provisions for a noon-conference-based curriculum, thus ensuring that didactic sessions are unaffected (2). However, being required to relinquish patient-care duties for the remaining 6–8 hours that residents used to work after a call night has raised concerns over continuity of care (6). These concerns seem especially valid for the general pediatrics service, where admissions for common problems such as dehydration, respiratory syncytial virus (RSV) and hyperbilirubinemia tend to be short. While the resident may gain valuable clinical experience from admitting the patient and providing the initial management, it is now likely that the child will be discharged even before the primary/admitting resident returns, thereby denying the house-staff the training experience that could have been achieved in caring for the patient.

This inability to examine the same patient over extended periods of time is of particular concern in pediatrics, as many of the most common admission diagnoses—most notably RSV and asthma—require frequent comparison to previous clinical examinations to effectively determine improvement. Not surprisingly, as a senior resident "cross-covering" on patients and not familiar with their initial presentation, I often resort to objective data to guide management, ordering further X-rays or blood work. Substantiating this anecdotal claim are studies indicating that cross-covering on patients increases length-of-stay and amount of test-ordering (7, 8).

Continuity of care is further compromised by the inability of physicians to follow clinic patients immediately after hospital discharge. Such follow-up was especially important in our residency program because it closely approximated how general pediatrics is practiced in community hospitals. Despite ACGME guidelines allowing for attendance at clinics in the six-hour post-call window, the guidelines also eliminate attendance at outpatient clinics on the afternoon following a call night, thus providing fewer opportunities to manage the child in the outpatient setting. Over three years of residency, this would translate to current interns having 1/4 to 1/3 less outpatient-continuity clinic exposure than those trained in a traditional program. It is unrealistic to deny these opportunities to current interns and still claim that the program will produce "the highest quality physician" (3).

But is this a trade-off at all? Several studies have found decreased performance on standardized tests after prolonged sleep loss (9, 10). It is not surprising that test scores, which use objective measures of cognitive skills, would decrease with the irritability and fatigue associated with sleep deprivation (11). What is not clearly defined is to what extent these observations directly translate into poor medical judgment. As early as 1971, Friedman and colleagues demonstrated that the ability to interpret an EKG decreases in sleep-deprived interns (12). Yet as we know from experience, an overnight call does not consist of a series of cognitive performances or a constant test of EKG interpretation. It is, rather, an exercise in:

a) Clinical evaluation of patients—Does this patient appear to be in distress and must these abnormal vital signs be acted upon acutely?
b) Information triage—Will the patient's test results, be it a chest X-ray, MRI or EEG, if obtained tonight, affect his or her management acutely?
c) Prioritization—There are three admissions and two calls from the wards. Who gets seen first?
d) Clinical skills—The patient needs a blood culture or an IV replaced.

Furthermore, the pace of an overnight session is often a key factor in the degree of fatigue the next morning. My personal experience (and those, anecdotally, of other house-staff) suggests that a call-night in which the resident is paged once an hour all night will result in less alertness than a steady, constant but manageable stream of work. Taking these parameters into account, Storer, in an evaluation of 45 pediatrics residents, found no decreases in the level of clinical knowledge, ability to obtain IV access or intubate, with sleep deprivation (13).

Current ACGME duty-hour requirements are partially derived from the 1987 *New York State Department of Health Ad Hoc Advisory Committee on Emergency Services Report on Supervision and Resident Working Conditions*, which originally outlined the 80-hour work week-limit and the consecutive 24-hour limit (14). This report resulted from a grand jury investigation into the death of Libby Zion, an 18-year-old woman who died in a New York City hospital in 1984. The grand jury cited five circumstances contributing to Zion's death, one of which was that her junior physicians admitted her at 2 AM, after 18 hours of work. However, this situation was still permissible under the new rules (15). Thus, the unfortunate clinical outcome that led to the new regulations can still occur in the context of new ACGME policies.

Also problematic is the fact that the "night-float" system constructed by many hospitals to conform to the New York State guidelines, has consistently been shown not to increase the total sleep time of residents (16). Yet the system still impedes continuity of care and disrupts the sense of autonomy that senior residents gain through training (17).

The waning sense of responsibility that house-staff physicians feel they have for cross-cover patients has been seen as straining the bond between patient and doctor (4). The best advice I received as a house officer came from a senior cardiology fellow, who told me, "Assume everyone else is trying to kill your patient." The implication was clear: Take responsibility for all aspects of your patient's care and be accountable for the actions you take to improve the patient's health. Increasingly, cross-coverage schemes and night float mechanisms disconnect the primary pediatrics resident from care, engendering a "shift-work" mentality in which doctors are trained to think of themselves as hourly wage professionals who provide a service to health-care consumers (15, 17). While this system may still provide adequate care for a self-reliant adult, it certainly is not the ideal model for pediatric medicine, in which the relationship between parent-child and physician is built up over the patient's childhood years. This is even more important as children reach adolescence, since they are less likely than adults to divulge risk-associated behaviors to physicians with whom they do not share a long-term bond.

Balancing the education obtained from long hours in the hospital setting with the exhaustion those hours cause is a daunting task for medical educators. To achieve competency in pediatrics one must witness a spectrum of clinical material. Yet one cannot be so fatigued that the lessons learned from seeing patients are lost. Pediatrics is unique among medical specialties in that its patients cannot be expected to advocate for themselves or offer complaints. Thus, the detection of many pediatric problems relies on frequent, serial physical assessments by house officers. The new national ACGME guidelines interrupt this pattern of patient care. Such disruption will no doubt detach house officers from patients, eroding personal responsibility in a young physician at a time when learning to be a child advocate is critical. Other unique factors of pediatrics, such as the short hospital stays and the prime importance of continuity of care, may also not be well suited for current duty-hour policies. Further experience under the new system will better demonstrate the effects of these rules on pediatric care.

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In Memoriam

Ruth Gail Abramson, M.D.

Ruth Gail Abramson, M.D., died on June 4, 2004 at the age of 70, as a result of ovarian cancer. She worked actively until about six weeks before her death.

Ruth arrived at Mount Sinai in 1963 and in 1987 became full professor in the division of Nephrology. She received her undergraduate education at the University of Pennsylvania and her medical degree at Downstate SUNY, where she was elected to Alpha Omega Alpha.

At MSSM she received various research awards, including the Hirschl Research Career Development Award. Her basic research into mechanisms of uric acid transport was supported by RO1 grants from the National Institutes of Health. The Alumni Association awarded her its highest honor, the Jacobi Medal. She also received the Faculty Council Award for Academic Excellence, and in 2003, she was named Distinguished Professor, a rare honor.

In informing the Mount Sinai community of her passing, Dean, President and CEO, Kenneth L. Davis, M.D., said, “There are few people who have displayed greater passion in caring for and protecting patients or more dedication to Mount Sinai. Her integrity, determination, intelligence and compassion will be sorely missed. Every day she challenged our entire community to live up to our highest values of caring, communicating, teaching and seeking new knowledge. She embodied our loftiest ideals and represented the best of Mount Sinai.”

A memorial service was held at MSSM on June 17, 2004. The speakers included Kenneth Davis; Dean Emeritus Nathan Kase; Medicine Chair Paul Klotman; CMO and EVP Deborah Marin; Nephrology Chief Barbara Murphy; Associate Dean for Research Jeff Silverstein; her former graduate student Dr. Joshua Rappoport; and Professors Terry Krulwich, Vesna Najfeld, and Sandra Masur. Her closest surviving relatives, her cousins Herb Abramson and Joseph Schnitzler, also spoke. (See: http://www.mssm.edu/wfg/CelebrateRuth.shtml)

Ruth’s scientific research was highly regarded—she is one of the few whose submissions to first rank peer-reviewed journals were accepted without revisions. As a clinician, she was also acknowledged as remarkable. Although she started her career when it was difficult for women in academic medicine, she overcame the barriers without outward signs of bitterness. She was a regular at the “doctors’ breakfast table” in the cafeteria—usually the only woman there.

She actively taught and mentored our students, fellows, and faculty members. To women scientists locally and nationally, she was a role model through her presidency of the Women in Nephrology, her research and her service on NIH study sections.

Colleagues who worked closely with her on the most sensitive issues commented that she was always compassionate to individuals, but strict in her adherence to her professional obligations. Dr. Davis noted that she was “the ultimate citizen of the medical center, she contributed greatly as a member and chair of numerous institutional committees. But her wise and effective leadership as chair of the Institutional Review Board was in a category of its own. She set standards of ethical conduct and effective administrative oversight that have been essential to the successful conduct of human subjects research at Mount Sinai.... She was uncompromising in her standards and never stopped inspiring her colleagues to strive for the same excellence. As an institution we owe her much.”

Ruth’s achievements enhanced the Mount Sinai Hospital and Medical School community, and the larger scientific community and society. Most important, she leaves a legacy of courage, integrity and caring that serves as a model for us all.

Sandra K. Masur, PhD
Professor of Ophthalmology
Associate Dean for Faculty Development
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THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 71 NUMBER 6 NOVEMBER 2004

CONTENTS

DEAN'S LECTURE

Molecular Signaling Regulating Anchorage-Independent Growth of Cancer Cells Lu-Hai Wang 361

GRAND ROUNDS

Using Community-Based Participatory Research to Reduce Health Disparities in East and Central Harlem Carol R. Horowitz, Agueda Arniella, Sherline James and Nina A. Bickell 368

Cardiovascular Disease in Diabetics: Pharmacology and Revascularization Sarang S. Mangalmurti and Michael E. Farkouh 375

GENERAL ARTICLES

Familial Polyposis Coli: Clinical Manifestations, Evaluation, Management and Treatment Govind Nandakumar, Jeffrey A. Morgan, Daniel Silverberg, and Randolph M. Steinhagen 384

Ethical Differences Between Socialized and HMO Systems Guest Editors: Martin H. Savitz and Michael M. Rivlin 392

Carpal Tunnel Release: Using a Short Vertical Incision above the Flexor Crease of the Wrist Avni Dayican, Vuslat Sema Unal, Suleyman Portakal, Ali Utkan, and Mehmet Ali Tumoz 401

Ultrastructural Changes in Rat Liver Treated with Pralidoxime Following Acute Organophosphate Poisoning Salim Satar, Deniz Satar, Ozgul Tap, Zikret Koseoglu and Mehmet Kaya 405

BOOK REVIEWS

Cardiac Pacemakers Step by Step: An Illustrated Guide Davendra Mehta 411

Peripheral Vascular Disease for Cardiologists: A Clinical Approach James Jang 411

Health Literacy: A Prescription to End Confusion Martin H. Savitz 413

Pharmacy Law Digest, 39th edition Peter Paxos 413

ABSTRACTS

Research in Medicine 2004—Mount Sinai School of Medicine 415

Research Day 2004—Queens Hospital Center 419

Annual Resident Research Day 2004—Jersey City Medical Center 424

List of Journal Reviewers in 2004 427

Author, Subject, Title Index to Volume 71 428

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Dean's Lecture

Molecular Signaling Regulating Anchorage-Independent Growth of Cancer Cells

LU-HAI WANG, PH.D.

Abstract

Normal adhering cells undergo apoptosis shortly after loss of adhesion to substratum, a phenomenon known as "anoikis." *In-vitro*-transformed cells and cancer-derived cells are able to survive and grow in the absence of anchorage to the extracellular matrix (ECM) and their neighboring cells. This represents one of the most important oncogenic properties of cancer cells. Integrin-ECM-mediated function is essential for survival and growth of normal adhering cells, while cancer cells are able to abrogate this requirement. This article will review and summarize the recent findings from our laboratory about the molecular signaling pathways important for the regulation of anchorage-independent survival and the growth of transformed fibroblasts and epithelial cells. Our study has shown that integrin-ECM-mediated signaling and cytoskeletal architecture play an essential role in effective recognition of the substrates by activated protein-tyrosine kinases (PTK) and their subsequent signaling functions. Among the various oncogenic PTK-activated pathways, phosphatidylinositol 3-kinase (PI3K)/Akt signaling is the most critical for anchorage-independent survival and growth. The activation of signal transducer and activator of transcription-3 (Stat3) and its function overlap partially with that of the PI3K/Akt in promoting anchorage-independent growth. Among the Rho family guanosine triphosphatases (GTPase), Cdc42, and to some extent Rac1, also appear to be important for promoting anchorage-independent growth.

Key Words: Anoikis, PI3 kinase, Stat3, Rho GTPases, anchorage.

Glossary

Akt: oncogene identified in the Akt-8 murine retrovirus isolation from an AKR/J mouse thymoma
Bad: a member of the bcl family apoptosis regulatory protein
ca: constitutively activated
ca PI3K: an activated PI3 kinase mutant
Cdk: cyclin-dependent kinase
CEF: chicken embryo fibroblasts
dn: dominant negative
ECM: extracellular matrix
EGF: epidermal growth factor
EGFR: EGF receptor
FAK: focal adhesion kinase
FKHRL1: forkhead-related transcription factor L1
GDP: guanosine diphosphate
GSK: glycogen synthase kinase
GTPase: guanosine triphosphatase
IGF-1: insulin-like growth factor-1
IGFR: IGF-1 receptor
ILK: integrin-linked kinase
IR: insulin receptor
JAK: Janus kinase
MAPK: mitogen-activated protein kinase
MC: methylcellulose
PI3K: phosphatidylinositol 3-kinase
PLCγ: phospholipase Cγ
PTK: protein-tyrosine kinase
RIE: rat intestinal epithelial
RPTK: receptor protein tyrosine kinase
Src: sarcoma-inducing gene in Rous sarcoma virus
STAT: signal transducers and activators of transcription
TGF: transforming growth factor

Introduction

ONE OF THE HALLMARK PROPERTIES of *in-vitro*-transformed cells and cancer cells is that they are capable of anchorage-independent growth. Normal cells require synergistic signaling func-

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tions elicited from growth factor-growth factor receptor interaction as well as from interaction between cell surface molecules and extracellular matrix (ECM), for survival and cell cycle progression (1). Complicated crosstalk and regulation takes place between the function of a growth factor receptor and integrin-ECM-mediated signaling (2–4). The important mitogenic signaling including mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and Rho family guanosine triphosphatases (GTPase) are known to be regulated by integrin-ECM signaling functions (2–7). Two integrin-associated protein kinases, focal adhesion kinase (FAK) and integrin-linked kinase (ILK), have been reported to play an important role in the process of crosstalk (8–10). Upon deprivation of substratum adhesion, normal fibroblasts undergo growth arrest, whereas normal epithelial cells undergo apoptosis, a phenomenon called "anoikis" (1, 11–13). The mechanism for the trigger of apoptosis in response to deprivation of cell adhesion to ECM is not clear, but it is likely to involve both the mitochondria and death-receptor-mediated activation of apoptotic caspases (11–13). There has been evidence to suggest that release of proapoptotic factors such as Bim and Bmf from cytoskeletal sequestration may play a role in the initial stage of the apoptotic process (14, 15). Transformed cells and cancer cells have reduced requirements for substratum adhesion and are able to survive and grow under the nonadhesive or anchorage-independent condition by inhibiting anoikis-related apoptotic pathways (11–13; Fig. 1). This *in vitro* property of cells correlates very well with their *in vivo* oncogenic potential. Therefore, one convenient assay of the potential of anchorage-independent growth, namely colony-forming ability in semisolid agar medium, becomes a reliable assessment of the oncogenic capability of cells. But what is the advantage for cancer cells of attaining such capability in the process of oncogenesis? One of the two most outstanding properties of cancer cells is uncontrolled growth and metastasis; the latter, in particular, defines the advanced stage and high malignancy of cancers. The metastatic process requires cancer cells to detach and migrate away from the primary tumor and to intravasate into blood or lymphatic vessels. The cells need to survive the anchorage-independent condition during the process, including their transportation through the circulation system until reaching a distant target organ, where they extravasate and begin to form initial metastasis. The migratory, invasive and anoikis-resistant capabilities of cancer cells endow them with the metastatic potential. Inhibiting these capabilities of cancer cells would effectively prevent the

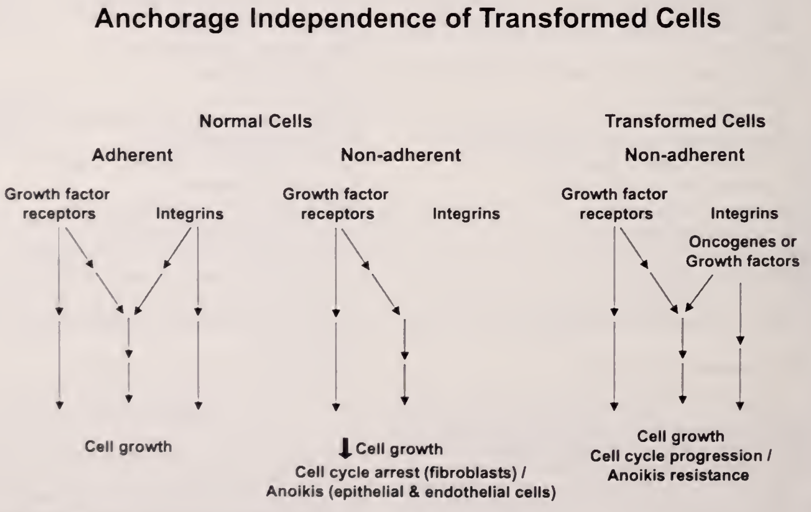
Anchorage Independence of Transformed Cells
Normal Cells
Transformed Cells
Adherent
Non-adherent
Non-adherent
Growth factor receptors
Integrins
Growth factor receptors
Integrins
Growth factor receptors
Integrins
Oncogenes or Growth factors
Cell growth
↓ Cell growth
Cell cycle arrest (fibroblasts) / Anoikis (epithelial & endothelial cells)
Cell growth
Cell cycle progression / Anoikis resistance

Figure. Anchorage independence of transformed cells.

process of metastasis formation. However, the molecular basis underlying these characteristics of cancer cells is not fully understood.

Do cancer cells constitutively activate certain signaling pathways to abrogate the requirement for integrin-ECM-mediated signaling function for survival and growth? Do those activated signaling pathways block the apoptosis process resulting from deprivation of adhesion and at the same time promote the cell cycle progression? What are the most critical signaling function(s) capable of sustaining survival and growth of cells under anchorage-independent conditions? This article will review and summarize some of the findings from our laboratory using certain activated receptor protein tyrosine kinase (RPTK) oncogenes in the transformation of fibroblasts and epithelial cells. Our results will be compared with those in the literature.

Anchorage-Independent Phosphorylation and Activation of PTK Substrates and Signaling Molecules

Normal protein-tyrosine kinases (PTK) initiate their signaling function upon cognate ligand binding in the case of receptor PTKs, or physiological activation in the case of nonreceptor PTKs, by autophosphorylation and phosphorylation of their immediate substrates and the signaling molecules. Oncogenic or activated PTKs essentially recognize and activate the same set of substrates and signaling molecules as their normal counterpart PTKs except at a higher intensity and constitutively. To assess the effect of ECM interaction and cytoskeletal architecture on substrate recognition by PTKs, we have adopted an anchorage-independent culturing condition by growing cells in methylcellulose (MC)-containing medium (16). Cells grown in the MC medium suspension can be readily recovered for protein analysis (16). Chicken embryo fibroblasts (CEF) expressing v-Ros, v-Src and v-Yes oncogenic PTKs were grown in monolayer or in the MC medium for 48 hours, and then compared for total cellular protein tyrosine phosphorylation by these oncogenic PTKs. The v-Ros is an oncogenic receptor PTK, whereas v-Src and v-Yes are two oncogenic nonreceptor PTKs; all have been derived from avian sarcoma retroviruses (17 – 19). The results revealed that, overall, tyrosine phosphorylation of cellular substrates was greatly reduced in cells grown in the MC medium compared to those grown in monolayer, despite the fact that the respective PTKs were equally abundant and active in cells grown in either adhering or nonadhering condition (16). All the mitogenic signaling pathways, including those of MAPK, phospholipase Cγ (PLCγ), PI3K, Stat3, E-cadherin and integrin/FAK were dramatically attenuated in nonadhering cells. However, PI3K and Stat3 remained significantly activated in v-Ros-transformed CEF when compared to control or transformation-defective v-Ros mutant expressing cells, suggesting that PI3K and Stat3 signaling may be important for v-Ros-induced, anchorage-independent growth (see below). A similar phenomenon was observed in rat intestinal epithelial (RIE) cells expressing an oncogenic insulin-like growth factor-1 (IGF-1) receptor or stimulated with epidermal growth factor (EGF) and grown under the adhering or nonadhering conditions (S. Uttamsingh and L.-H. Wang, unpublished). Addition of ECM molecules such as fibronectin, laminin, collagens or Matrigel (Sigma, St. Louis, Missouri) to the semisolid medium did not correct the inability of those activated PTKs to recognize and activate their substrates and downstream signaling molecules when cells are grown under the nonadhering condition. These results indicate that cell-ECM interaction and spatial architecture of the cytoskeleton are critical for PTKs to be able to effectively interact and phosphorylate their substrates and initiate the signaling functions. This is true not only in normal cells, but also in the transformed cells expressing constitutively activated PTKs. Our results are consistent with the well-established link between integrin signaling and activation of Ras-Raf-MAPK pathway (3, 4, 9, 20). Integrin-ECM-mediated signaling is able to amplify and prolong the growth factor receptors-mediated mitogenic signaling. Thus, integrin/ECM signaling and cytoskeletal structure appear to play a critical role in properly positioning the substrate molecules for their recognition and activation by PTKs and in subsequent augmenting of the signaling process.

Role of PI3 Kinase/Akt Signaling in Anchorage-Independent Growth

The PI3K pathway can be activated by different mechanisms, mainly via growth factor receptors and integrin/ECM-mediated signaling, and it plays an important role in a multitude of cellular functions, including cell growth, survival, migration and invasion (21 – 24). Using the NIH3T3, CEF and RIE cells as well as the MC medium culturing system, we examined the role of PI3K/Akt (see glossary) signaling in anchorage-independent growth. Our results showed that the oncogenic insulin receptor (IR) and IGF-1 receptor (IGFR)-transformed RIE cells were inhibited by the PI3 kinase inhibitor LY 294002 and the p70S6 kinase inhibitor rapamycin for their ability to form colonies in semisolid agar medium (25). By contrast, Src-transformed (see glossary) RIE cells were relatively resistant to the similar inhibitors for colony formation, suggesting that Src apparently was able to activate certain pathway(s) with a function redundant to that of PI3K/Akt for anchorage-independent survival. Similarly, v-Ros-transformed CEF or activated EGFR-Ros-chimera-expressing NIH3T3 cells were highly sensitive to the inhibitors of PI3K and p70S6 kinase for colony formation (26). Inhibition of the colony-forming ability by pharmacological inhibitors of the PI3K-signaling molecules was confirmed by transfection and expression of the dominant negative (dn) mutants of PI3K and Akt in those transformed cells (26). Conversely, activated PI3K was able to rescue the colony-promoting activity of two transformation-defective mutants of v-Ros (26). The colony-forming ability of NIH3T3, CEF and RIE cells expressing those activated PTKs, by contrast, was relatively resistant to inhibitors of the MAP kinase (25, 26). Interestingly, Vav3, the third member of the Vav family Rho GTPases nucleotide exchange factors, upon its activation, was able to promote the evasion of contact inhibition (i.e., focus formation) in NIH3T3 cells efficiently, but was unable to promote their anchorage-independent growth in soft agar (27, 28). Upon screening of a number of activated molecules involved in mitogenic signaling functions, an activated PI3 kinase mutant (caPI3K) was found to be able to cooperate with the activated Vav3 for promoting colony formation of the NIH3T3 cells, while neither activated Vav3 nor caPI3K alone was able to do so (28). It would be interesting to identify which signaling function of Vav3 is involved in such collaboration. Our observations are consistent with those in the literature demonstrating the importance of PI3K activation and signaling in various oncogene-transformed cells and in cancer-derived cells (29 – 35).

How does PI3K signaling promote the anchorage-independent growth? The effect of activated PI3K on anchorage-independent expression and activation of cells-cycle-regulatory proteins was investigated. While expression of various cyclins and cyclin-dependent kinases (Cdk) was not affected in v-Ros-expressing CEF under nonadhering conditions, the cyclin-A-associated Cdk activity appeared to be augmented in the v-Ros-expressing CEF, but not in the control or v-Ros mutant-expressing cells (16). The increase in cyclin-A-associated Cdk activity was PI3K dependent, since it was blocked by the PI3K inhibitor. The PI3K-dependent increase of Cdk2 activity was important for v-Ros-induced colony formation, since inhibition of the Cdk2 activity to the level of control CEF blocked the colony-forming ability of v-Ros-expressing cells (16).

In another study, we showed that EGF and transforming growth factor (TGF)-β1 synergistically protect RIE cells from anoikis, which was also blocked by PI3K inhibitors (S. Uttamsingh and L.-H. Wang, unpublished). Activation of MAPK and Akt was prolonged in the EGF- and TGF-β1-treated cells grown under nonadhering conditions, leading to phosphorylation and inactivation of pro-apoptotic proteins such as glycogen synthase kinase (GSK)-3β and forkhead-related transcription factor L1 (FKHRL1) as well as decreased level of cyclin inhibitor p27^{KIP1} and p16^{INK4a} (S Uttamsingh, KT Nguyen and L-H Wang, unpublished). Taken together, PI3K signaling appears to be able to block the apoptotic process and enhance the anchorage-independent cell cycle progression at the same time. Akt was previously shown to phosphorylate directly or indirectly and inactivate pro-apoptotic proteins such as caspase 9, Bad (see glossary) and FKHRL1 in different cell systems (36 – 43). Our results are consistent with those findings. Overall, the activated PI3 kinase signaling plays a critical role in protecting cells from anoikis by inactivating certain key apoptotic molecules and at the same time enhancing anchorage-independent cell cycle progression by inhibiting the cyclin inhibitors and enhancing certain Cdk activity.

The Role of STAT Signaling in Anchorage-Independent Growth

Among the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling components, Stat3 stands out for its involvement in regulating cell growth and transformation as opposed to cell maturation, cell stress and acute phase responses for most of the other STAT signaling functions (44 – 46). Stat3 was initially found to be activated in Src-transformed cells (47). Subsequently, activation and signaling of Stat3 was shown to be important for cell transformation by several oncogenes (48 – 51). Moreover, constitutively activated Stat3 alone was demonstrated to have a considerable degree of transforming and tumorigenic potential (52). A variety of naturally occurring cancer cells have been shown to harbor an elevated level of Stat3 or an elevated level of activated Stat3 (53–59). Those observations firmly place Stat3 on the list of pro-oncogenic molecules. However, its precise role in oncogenesis in general and in anchorage-independent growth in particular remains unclear. We showed that activation of Stat3 was required for EGF receptor (EGFR)-Ros- and oncogenic IGF-1R-induced anchorage-independent growth of NIH3T3 cells (50). As mentioned above, activation of Stat3 and PI3K stand out as providing two enhanced signaling pathways in v-Ros-expressing cells maintained under the nonadhering conditions. Both signaling pathways were shown to be important for v-Ros-mediated anchorage-independent growth. The dn Stat3 and dn PI3K additively inhibited v-Ros-induced colony formation of CEF. Conversely, the ca Stat3 and ca PI3K additively rescued the colony-promoting activity of two transformation-defective mutants of v-Ros. The ca Stat3 was able to partially rescue the inhibition of EGFR-Ros-induced colony formation of NIH3T3 cells by PI3K inhibitor LY294002 (26). Those observations suggest that the Stat3 signaling function partially overlaps with that of PI3 kinase in promoting anchorage-independent growth. The mechanism by which Stat3 signaling actually leads to promoting anchorage-independent growth is not clear. However, it was shown that activation of Stat3 was accompanied by the upregulation of cyclin D1, c-myc and Bclx (58), whose changes are consistent with the protection of cells from anoikis and promotion of anchorage-independent cell cycle progression. Nevertheless, direct evidence for those molecules in mediating Stat3-induced colony formation and cell transformation awaits further study.

Role of the Rho Family GTPases in Anchorage-Independent Growth

All members of the small GTP-binding GTPases superfamily exist in cells as either the inactive guanosine diphosphate (GDP)-bound or the active GTP-bound form, the latter of which is regulated positively by nucleotide exchange factors and negatively by GTPase-activating proteins (60, 61). The most well-studied members of the Rho family GTPases are RhoA, Rac1 and Cdc42, which were initially known for their function in regulating the formation of stress fibers, lamellipodia and filopodia, respectively (62–65). Subsequently, they were shown to be involved in other cellular functions as well, notably cell growth, motility and transformation (62–71). While Rho GTPases function to regulate cytoskeleton, they are themselves regulated by integrin signaling (72–75). Using the same cell and oncogene systems described above, we have examined the roles of Rho, Rac and Cdc42 in cell transformation including anchorage-independent growth. Using an oncogenic IGFR and its loss-of-function mutants, we analyzed the roles of Rho, Rac and Cdc42 in this oncogenic IGFR-induced transformation of NIH3T3 cells (69). Our results indicated that those GTPases played distinct roles in the oncogenic IGFR-induced evasion of contact inhibition (assayed by focus formation) vs. anchorage-independent growth (assayed by colony formation). Dominant negative (dn) Rho most potently inhibited focus formation of the cells, whereas dn Cdc42 inhibited colony formation most effectively among the three GTPases. Conversely, constitutively activated (ca) Rho rescued the focus-forming ability of the IGFR mutants, while ca Cdc42 rescued their colony-forming ability most efficiently. Thus, Rho signaling appears to play a more important role for evasion of contact inhibition, whereas Cdc42 signaling is more important in promoting anchorage-independent growth. This conclusion about the role of Cdc42 in anchorage-independent growth is consistent with the reports that Cdc42 mediated integrin signaling for activation of PI3 kinase and Akt (76, 77). The observation of the importance of Rho for focus formation was supported by one of our other studies, where we observed that Vav3-induced focus formation of NIH3T3 cells was most potently inhibited by dn Rho (28). Cdc42 most likely promotes anchorage-independent growth via activation of Rac, PI3K and Akt. The mechanism for Rho-mediated evasion of contact inhibition remains an intriguing open question.

Conclusion

Integrin/ECM signaling plays a critical role for growth and survival of normal adhering cells. Deprivation of anchorage destines cells to undergo growth arrest and apoptosis. Cancer cells are able to survive the lack of anchorage, and thus the lack of integrin signaling, by preventing the apoptosis process. This occurs because of the intrinsic constitutive activation of certain signaling pathway(s), notably those of the PI3K, Stat3 and GTPases, discussed above. While activation of mitogenic and pro-survival signaling can logically explain the anchorage-independent growth of cancer cells, it is quite plausible that mutation and inactivation of tumor suppressors and pro-apoptotic factors in cancer cells could endow them with similar oncogenic ability. This possibility is not discussed here. Other signaling functions, such as Ras/Raf/MAPK and PKC pathways, which are likewise not discussed here, may also help promote anchorage-independent growth. Nevertheless, the PI3 kinase/Akt is apparently the converging point and is the key signaling function for survival. To date, we have not observed a single oncogene transformed or a cancer-derived cell line that is able to undergo anchorage-independent growth when PI3K/Akt function is blocked, with the exception of Src-transformed RIE cells (mentioned above), which are partially resistant to the inhibition of PI3 kinase (25). This could be explained in part by the fact that Src is a potent activator of Stat3 (47) and our evidence has suggested that Stat3 signaling is able to compensate partially for the lack of PI3K/Akt function for anchorage-independent growth (26, see above). Therefore, both Stat3 and PI3K/Akt, especially the latter, are important and prudent molecular targets for anti-cancer intervention.

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Grand Rounds

Using Community-Based Participatory Research to Reduce Health Disparities in East and Central Harlem

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Abstract

Objective: It is important to teach community members about the causes, magnitude and effects of health disparities that affect them, and to partner with them to develop, test and disseminate programs that they can sustain to improve health. East and Central Harlem are two underserved, predominantly minority, inner-city communities whose residents have disproportionately high morbidity and mortality from chronic conditions. We developed an approach to educate and work together with Harlem residents to study health disparities, and to use peer-led classes to improve chronic disease management and outcomes.

Methods: Researchers and community leaders formed a community-based research core ("Core") with funds from a large health disparities grant. We then assembled a community advisory board and partnered with them to start a community newsletter to explain the causes of local health disparities and suggest ways to eliminate them. Together, we also began to create a self-sustaining cadre of community-based peer educators to teach culturally acceptable chronic disease self-management skills.

Results: The recruited board consists of 33 leaders of community-based health and social service organizations, religious institutions, and tenant organizations, as well as local activists. We produced and distributed our first educational newsletter to more than 4,000 community leaders, members and community-based organizations. We also adapted an existing chronic disease self-management program for the Harlem population and developed strategies to recruit peer educators and sustain their efforts in the future. To help them attain expertise in teaching chronic disease self-management, the board selected four individuals to become master peer-education trainers. The board then helped recruit more than 60 community members and leaders for our first two peer-education courses.

Conclusions: Researchers, clinicians and community leaders worked together to disseminate knowledge about health disparities and a peer-organized education program to address these disparities. This approach provides a foundation to attain a cadre of community-based experts to inform the community about ways to reduce health disparities. By pooling local and academic expertise and resources, we hope to develop programs that are workable, effective and sustainable without outside control or funding.

Key Words: Health disparities, community, self-management, African-American, Latino, community-based participatory research, chronic disease, grants.

Introduction

Racial disparities in health and health care continue to plague our society (1). Following years of research documenting the existence of such disparities, the focus is now on finding interventions to eliminate these differences. Community-based participatory research (CBPR) offers an opportunity to redress health disparities in communities. CBPR is equitable involvement between researchers and those affected by the issue under study in all aspects of a research process, aiming to improve health, generate knowledge and effect social change, and includes recognizing the social, economic and political systems that shape health behaviors and access to resources needed to maintain health (2). It also includes designing community health programs that address differences in cultures, health beliefs and disease presentations, which may result in substandard care for individuals or groups (3).

Although communities and health care systems often have historical reasons for mistrust and misgivings about each other, both can ben-

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efit from envisioning each other as partners with important expertise and resources (4). Together, researchers and community leaders can develop workable, sustainable programs that target a population's needs, ensure cultural appropriateness, and evaluate and disseminate the results (5). Collaboration in CBPR is a partnership among equals with unique and complementary knowledge or expertise (6). This research begins with a topic of importance to the community, and aims to combine knowledge with action, to improve health outcomes and eliminate disparities. CBPR motivates co-learning and sharing expertise by researchers and community members. It differs from more traditional community-placed research, which favors work conducted in a community setting, but with limited community involvement (6).

East Harlem (also called Spanish Harlem or el Barrio) and Central Harlem in New York City have a combined population of approximately 228,500 people, 34% of whom are low-income Hispanics (predominantly Puerto Rican) and 57% African Americans (7). Recent migration changes have seen the growth of new enclaves of immigrants from Mexico and Central America. Harlem has a long history as a cultural center, because of its ethnic diversity and its prominence in American arts and culture. Much of this cultural richness still remains and is now being revitalized, with recent initiatives such as the Federal Empowerment Zone. However, 36% of Harlem residents live in poverty (7). Although East and Central Harlem house two municipal hospitals, one community hospital, one tertiary-care medical center, and many community health clinics, their residents have the highest rates of cerebrovascular deaths, infant mortality, cancer deaths and all-cause mortality in New York City (8). Mortality rates for Central Harlem in 1980 were not only the highest in New York City, but also more than double those of U.S. whites and 50% higher than those of U.S. African Americans. African American men in Harlem at that time were less likely to reach age 65 than were men in Bangladesh (9). Moreover, there are still great disparities between health outcomes in Harlem and in the adjacent Upper East Side, whose population of approximately 216,400 is 91% non-Hispanic white (7). The Upper East Side has the lowest poverty rate (6%) and the lowest death rates for the above conditions in New York City (8).

Utilizing the principles of community-based participatory research, we aimed to reduce such disparities by addressing the specific challenges of the Harlem community with practical, sustainable, culturally appropriate solutions that utilize the community's strengths, and whose effectiveness can be tested by rigorous research methods. The Harlems (typical of many minority communities) have lacked adequate research expertise, funding, and active community input devoted to providing better care for people with the typical health care problems in these communities. We therefore applied for and received a federally funded EXPORT (**EX**cellence in **P**artnering for Community **O**utreach **R**esearch on Health Disparities and **T**raining) center grant to establish a center where researchers, community residents, policymakers and clinicians could put their combined strengths to use in eliminating health disparities. Over time, we expect these efforts to generate innovative programs and collaborations with clear results, and inspire a new generation of community leaders and researchers to help eliminate health disparities and develop community-based programs to do so. We also aim to devise ways of maintaining successful activities after funding has been terminated.

We actively involve community members in efforts to educate the community about the prevalence and causes of racial and ethnic health disparities, and potential strategies to eliminate them. Specifically, we partner with Harlem leaders to recruit and teach local individuals with chronic diseases to become peer educators who can then teach other community members self-management skills for their chronic illnesses. These skills have been adapted to the ethnic, cultural, and social environment in Harlem. Self-management education is a critical ingredient of appropriate health services, especially for the African-American and Latino populations. That is because these groups, in addition to carrying a heavy burden of illnesses, encounter limited access to health care and to health education due to economic, language and cultural barriers (10). The "Chronic Disease Self-Management Program" is a peer-led self-management program utilizing groups that include patients with different chronic diseases. The program improves patients' self-management skills, increases their perceived ability to manage their conditions and the demands of everyday life, improves their health status, and facilitates their more effective use of health care services (11).

Through six $2^{1}/_{2}$-hour-long classes, the program teaches patients how to take the initiative for their own health care and their dealings with health personnel, clarifies the use of family and community support systems, and builds on patients' relationships with providers and institutions. The program has been proven effective in reducing patients' symptoms, emergency visits and costs, and in improving ability to function, among people with symptomatic chronic diseases (12). Our goals were to adapt this program to the populations of Harlem, base it in the community rather than in health institutions, and identify community members to be trained as peer self-management educators. The peer-education classes will be tested through research and made available throughout the community as a service. Using this strategy, we aim to create a self-sustaining cadre of community-based experts in chronic disease self-management techniques and training. In this paper, we will describe our approach, thereby providing a concrete example that can be used by other clinicians and researchers, as a way to begin partnering and actively working with community members to improve local health.

Methods

To address health disparities in Harlem, we formed a community outreach and information dissemination core ("Core") as part of the EXPORT Center grant. The Core's goals were to establish and maintain meaningful community partnership and expertise, with a focus on improving the delivery of effective health care to residents of Harlem. We carefully selected an interdisciplinary leadership team to build on the strengths and experiences of community leaders, clinicians and researchers. All members have extensive experience working in Harlem and building academic-community collaborations (13).

Grant-proposal-writing itself was used as a method to build partnerships and trust, and to share ideas. Through a series of meetings, Core leaders agreed on a set of objectives, and methods to accomplish these goals. We also wrote a detailed education plan to involve the community in building, leading and sustaining peer-led self-management classes. Our planned dissemination strategy included developing both a community newsletter and a series of community lectures and discussions. We used grant proposal "letters of support" to begin dialogues with community leaders about our shared aims, thereby garnering wider community commitment from the outset. These letters became statements of mutual commitment—for the Core team to involve supporters, and for supporters to actively work with us, if the grant were funded.

Once funding began, we informed all persons who wrote support letters that we were ready to begin our work, and gave them a summary of what we planned to accomplish. First, the Core co-directors (a white clinician and researcher, and an African-American health activist), began to form an EXPORT community advisory board ("Board"). We sought persons who had extensive experience in Harlem, could communicate easily with community and health leaders, and possessed an intimate understanding of the community's social networks and assets. All the individuals from community-based organizations, churches, tenant associations, health centers and local businesses, as well as the community activists who were invited, agreed to join the Board. Recruiting such persons is the cornerstone of community health advisor programs that aim to improve the health status of underserved communities and increase their access to health care and social services (14, 15).

The Board meets on a quarterly basis to deepen their involvement in the EXPORT Center. We "assigned" each Board member to one of the Core leaders, so that the leaders would regularly stay in contact with them between quarterly Board meetings. During Board meetings, Center researchers and clinicians update the Board about the Center's recent activities, and elicit their advice and feedback. Community leaders present ideas for projects to help reduce health disparities among people in Harlem. The Board has formed a peer-education subcommittee and a newsletter subcommittee. Through these two subcommittees, the Board works to implement its education and dissemination strategies.

The newsletter, ECHHO (**E**ast and **C**entral **H**arlem **H**ealth **O**utcomes), co-written by researchers and community leaders, contains articles that focus on health disparities and programs in Harlem that address them. The newsletter subcommittee of the Board became the editorial board, and appointed two co-editors, a researcher and a community leader. The newsletter contains articles that are co-written by a researcher and community leader, to foster sharing of expertise, communication, understanding, respect and trust. Through collaborations, the subcommittee aimed to bridge the gap between members of academia and members of the community. The newsletters, distributed to more than 4,000 community leaders and community members, help keep the community informed of and involved in the Center's plans and activities. The results below will highlight the strategy we employed to build partnerships that lead to a sustainable program in which local residents are expert peer educators and teach skills to improve the self-management of chronic diseases.

Results

We identified and recruited 33 leaders of community-based health and social service organizations, religious institutions, and seniors' and tenants' organizations, as well as local activists, to form our community advisory board. Through quarterly meetings, and frequent subcommittee meetings, the predominantly white researchers and predominantly non-white community leaders began to understand and respect each other's expertise and perspectives. Community leaders, some of whom joined the board as a favor rather than an opportunity, came to appreciate the complexity of planning and implementing a large-scale research project. They also appreciated the commitment researchers had to working with them in their community on a long-term basis. In addition, they stayed actively involved because they had subcommittee responsibilities and were therefore essential team members, not bystanders. Researchers, some of whom viewed the Board as an obligation rather than an opportunity, learned the depth and breadth of existing local programs to target racial and ethnic disparities, and the extent of Board members' expertise in issues relating to the local community's health.

As we learned to work smoothly with the Board, we tailored the peer-education program to the predominantly African-American and Latino adults who reside in Harlem. For example, community leaders strongly recommended that the program acknowledge and provide opportunities to discuss the effects of poverty, racism, and perceived substandard health care and housing on residents' health and well-being (16). We therefore worked with the developers of the program to modify the program to allow for discussions of these and other local issues. Next, we chose four persons from the community to undergo a one-week-long training course to become "master trainers" who could lead programs and train community members to lead the programs.

We then needed to train community members to conduct peer-education groups. To do this, we chose to identify community members with chronic diseases to attend peer-education groups and invite them to become peer leaders. The Board's peer education subcommittee worked with Core leaders to build a recruitment strategy. Core leaders contacted their "assigned" Board members, each an emissary of a community-based organization, and asked them to nominate one or two of their constituents (or themselves) who had chronic diseases and wished to learn self-management skills, to attend one of two classes. We also contacted others who had sent us letters of support, to "keep our promise" that we would work with them to accomplish the aims they had agreed to support. In this way, we sought both to garner community support and to firmly establish the peer-education program in the community from its outset.

The process of identifying peer-group members and potential leaders was delayed, as community leaders learned first hand about the necessity of receiving Institutional Review Board approval and obtaining informed consent from the group members, who were also potential research subjects. Core community members also worked intensely with researchers, who were concerned that community recruitment would compromise an impending randomized trial to test the effectiveness of the program. Community members expressed their concern that the narrow parameters for inclusion in the randomized trial would exclude many community members, thereby deepening local cynicism and mistrust of the program and damaging potential to disseminate and sustain the program in the future. They were also concerned that researchers planned to hold two community classes and that all remaining courses would only include research. Based on these concerns, researchers agreed to allow community partners to host the classes at their sites, and have research subjects join community classes. Core leaders and researchers successfully wrote a document that outlined a compromise that all were comfortable with, and used this to communicate with other researchers and members of the Board. Researchers were pleased they decided to adopt community leaders' recommendations when these leaders moved from being reluctant to recommend potential participants to enthusiastically offering to hold classes and recruit participants.

To date, 78 participants attended the fist 6 classes and 11 organizations have agreed to host classes. A major goal of these first classes is to identify individuals who wish to become lay leaders and teach their own classes. Therefore, those who complete these courses and are considered potential peer-education leaders will be invited to a 4-day peer-leader training course. They will be paid for their time to take this course, and for their future work if they lead sessions that are part of the randomized-trial research study of the peer groups. By "embedding" these leaders in the community, the Board is creating an ongoing, sustainable resource.

Discussion

By bringing together a diverse group of community-based organizations and activists to write a grant proposal to eliminate racial health disparities in their communities, we established the foundations of an ongoing relationship dedicated to educating and disseminating information about ways to reduce health disparities in Harlem. Together, individuals from health and social services, community-based religious institutions and seniors' and tenants' organizations, as well as local activists and researchers joined to educate members of the community about chronic disease self-management skills. Several Board members plan to be trained as peer-education group leaders, so that they can bring this service back to their constituencies and become an integral part of this sustainable service. They are thereby developing a potentially sustainable community resource of individuals skilled to train additional community residents in the future. By using a community-based participatory approach, we have been able to develop and strengthen the trust between groups of individuals who historically have reasons for mistrust. We have also built on the momentum developed during the grant writing and on the positive relationships between researchers and community members, to engage our community advisory board, and enroll community residents for peer-education training and contributions to our newsletter.

We have taken steps to demystify the research process among community members. Community members have become advisors or collaborators in ongoing, funded research projects, enhancing the cultural competency of the research, adding new strategies, assisting in patient recruitment and retention, and developing culturally sensitive information for community members. They also sharpen their presentation skills for clinical, scientific and public health and policy audiences by presenting at committee meetings and local governmental hearings, co-presenting with researchers at local and regional meetings, and writing articles in the newsletter. In fact, the writing of this paper is an integral part of CBPR.

We have also taken steps to encourage researchers to incorporate CBPR principles and practices into their research projects. By actively participating in the Board's activities and in working groups with community leaders, researchers have also gained a better understanding of the communities' perspectives on research, disparities and factors relating to disparities. Researchers now regularly rely on Board members' advice to develop and conduct research implementation strategies. Through community presentations and writing for the newsletter, researchers are becoming more adept at communicating with residents of Harlem. These skills will help researchers disseminate their new knowledge to the community as well as to other researchers and clinicians. As we work together to write articles and give joint presentations of this work, each group becomes more sensitive to the other's perspective, and more able to portray that perspective to audiences.

Most programs to improve health in minority communities such as Harlem are developed by persons from outside the target communities, without direct input from members of these communities (17, 18). Interventions created solely by outsiders may perpetuate the inequalities that well-meaning researchers aim to address, create an atmosphere that discourages community experts from sharing invaluable perspectives and ideas, and thwart the entry of researchers and their projects into the communities. By contrast, we built strong relationships with many community leaders, who have helped ensure that our project goals and the means of accomplishing them are relevant and sensible for the targeted Harlem population (19), and that the work conducted under the auspices or the grant will continue beyond the grant-funded cycle. Through mutually respectful relationships, with shared responsibilities, communities and researchers can increase the community's capacity to identify and solve its own problems (20). Through their experiences, the leaders of this community Core have learned how to successfully engage communities in research endeavors, and communicate with community members in a culturally sensitive manner. We hope these partnerships will be sustained and expanded in other research and community endeavors.

Researchers usually have ad-hoc relationships with community members that last only for the duration of the projects. Only sustained involvement during the project can equip community members with the knowledge and skills they need to meaningfully participate in studies as more than research subjects. Lack of involvement, on the other hand, can increase community mistrust of research and researchers, and thwart future collaborative efforts (21, 22). Equally important, it can cause researchers to lose an invaluable opportunity to partner with community experts to make their research more relevant, practical, focused and sustainable. We hope that through our dissemination strategies, we will help other researchers solidify relationships with communities and community leaders.

Like other collaborative research teams, we have faced challenges. Successful academic-community partnerships build trusting relationships over time (23). Our partners have different perspectives on the relative importance of processes vs. outcomes, research vs. service, and the need for rigorous evaluation. They also have different styles of communication and decision making, and different opinions of who may legitimately represent the community (24). By establishing common goals and ground rules that promote understanding, communication and respect, and outlining how decisions will be made, our coalition is thriving despite these tensions (25). The message and mission of the coalition is strengthened through active participation, listening and responding to the needs of coalition partners, and capitalizing on strengths rather than focusing on deficiencies of the community. Through this process, we have begun to gain credibility in both the community and academic institutions (26). By establishing a Board and fostering peer-recruitment activities, we are building on existing working relationships and trust to allow us to rapidly mobilize resources and move from planning to implementation (27). We began by explicitly acknowledging the community's mistrust or "healthy paranoia" of researchers and outside organizations, given the history of racism, marginalization of minority communities by health care systems, and past experiences of having researchers enter communities or health centers, collect data, provide no direct benefits, and leave without giving feedback or taking noticeable actions (21, 22, 28).

Our project is still in its early phases. It is too soon to determine whether we have been successful in creating a sustainable cadre of community-based expert teachers of chronic disease self-management. We are working to sustain the peer-educator program in two ways. First, as part of community faculty development, Center personnel will mentor community leaders to write grant proposals to governmental or private organizations that could fund a peer-group coordinator, peer educators, or peer-education. Second, faculty will work with individual agencies to continue conducting groups. We believe that through simple steps, including involving community leaders in a project from its outset, having an active community-advisory board, providing opportunities for health and community experts to openly communicate and respectfully share expertise and responsibilities, and creating and following a plan to sustain promising programs after grant funding has ended, researchers and clinicians can deepen the meaning and effectiveness of their efforts to eliminate health disparities.

Conclusion

Community-based participatory research optimally takes place through a collaborative process, from grant-proposal-writing through the conduction and planning of research. Through these efforts, we discover the needs and goals of the community, clarify what can and cannot be accomplished, and build mutual trust and respect among researchers and community leaders. This process can further empower communities by using research funding to train community members to utilize effective methods to improve their health, thereby bringing an important, sustainable service to the community.

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Cardiovascular Disease in Diabetics:

Pharmacology and Revascularization

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Abstract

Diabetes has become a public health crisis. With the incidence of obesity rising in the United States, the number of diabetics will grow considerably. Of greatest concern is the impact this trend will have on cardiovascular disease. Diabetics demonstrate accelerated coronary atherosclerosis, and the prognosis is worse following cardiac events. Moreover, our interventions have achieved uneven success in treating this subset of patients. This paper will review the metabolic abnormalities that promote atherosclerosis in diabetics and the current methods for treating and preventing the development of coronary artery disease in diabetics, principally through a combination of medications and revascularization.

Key Words: Diabetes, cardiovascular disease, insulin resistance, antiplatelet, dyslipidemia, hypertension, myocardial infarction, acute coronary syndrome, revascularization.

Introduction

DIABETES HAS BECOME a public health crisis. With the incidence of obesity rising in the United States, the prevalence of diabetes is expected to grow from 16 million cases to an estimated 22 million by 2025 (1). The effect of this on cardiovascular disease is unquestionable. Diabetic men have a threefold increase in the risk of cardiac disease compared to nondiabetics. And studies have shown that diabetics with no prior myocardial infarction have a risk of infarction similar to that of nondiabetics with a history of myocardial events (2); see Fig. 1 (3). Diabetic women are especially vulnerable and appear to lose their premenopausal protection from coronary artery disease (4). Unfortunately, our measures against cardiovascular disease have seen a smaller decline in cardiovascular mortality for diabetics compared to the general population.

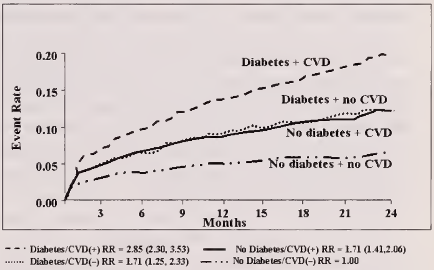

Fig. 1. Event rates, RR and CI for cardiovascular death (CVD) in diabetics and nondiabetics (n=8,013) with and without a history of CVD after hospitalization for coronary syndromes. RR = relative risk, CI = 95% confidence interval (3).

Since more than 90% of diabetics are type 2, our prevention strategies begin by targeting the constellation of metabolic derangements seen in these patients, collectively called "syndrome X" or the cardiovascular dysmetabolic syndrome (5). These include insulin resistance (from impaired glucose tolerance to hyperglycemia), dyslipidemia, hypercoagulability, and hypertension. Multiple drugs are utilized to slow the progression of atherogenesis in these patients. And the onset of symptomatic coronary artery disease heralds the need for revascularization, often with varying results in diabetics. The following discussion will review the metabolic predisposition to atherosclerosis in diabetics and highlight the pharmacologic and

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revascularization options that comprise their medical management.

Hyperglycemia

Hyperglycemia as a cause of vascular disease has been observed experimentally in animal models, and clinically through the benefits of tight glucose regulation. The Diabetes Control and Complications Trial (DCCT) demonstrated that aggressive glycemic control in type 1 diabetics reduces the risk of microvascular complications including retinopathy, microalbuminuria, and clinical neuropathy by 76%, 39%, and 60%, respectively (6). A similar trend was seen in type 2 diabetics in the United Kingdom Prospective Diabetes Study (UKPDS), where fasting glucose levels of less than 108 mg/dL resulted in a 25% reduction in the risk of microvascular disease over 10 years (7).

The link between hyperglycemia and macrovascular disease, which was not clearly demonstrated in these large trials, has been shown in smaller studies. The San Antonio Heart Study showed a proportional increase in cardiovascular-related deaths with higher fasting blood glucose levels in type 2 diabetics (8). A similar result appeared for type I diabetics in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, where patients were followed for 10 years and demonstrated an 18% increase in cardiovascular mortality and a 1% increase in glycosylated hemoglobin (9).

Insulin Resistance

For type 2 diabetics the presence of insulin resistance and hyperinsulinemia accelerates the development of atherosclerosis. One study showed hyperinsulinemia as an independent risk factor when adjusted for lipid profile, hypertension and family history (10). Studies of multiple ethnic groups have shown increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance (11). Furthermore, impaired glucose tolerance (IGT), even without frank hyperglycemia, can increase the risk of heart disease (12). Since insulin resistance can precede clinically diagnosed diabetes by 10–15 years, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics.

There are multiple pharmacologic options for these patients, each utilizing a different mechanism for lowering blood glucose levels. The major classes of drugs include: thiazolidinediones (troglitazone, rosiglitazone, pioglitazone); biguanides (metformin); and insulin secretagogues (sulfonylureas, repaglinide).

The thiazolidinediones act in the nucleus of muscle and adipose tissue to increase transcription and translation of surface glucose transporters. This augments insulin-mediated uptake of glucose, reducing glycosylated hemoglobin levels by as much as 1.5% (13). By sensitizing the action of circulating insulin, daily insulin requirements are reduced, sometimes by 50%, and the risk of hypoglycemia is lowered compared to other diabetic agents. Although these agents increase low-density lipoprotein (LDL) levels, they reduce triglycerides and small, dense LDLs (which are atherogenic), while raising high-density protein (HDL) levels and minimizing harmful oxidative changes to normal LDL (14). Disadvantages of this therapy include hepatotoxicity, weight gain, fluid retention and slow onset of action, with lowest glucose levels achieved 6–8 weeks after initiating therapy. All three thiazolidinediones are felt to be safe and equally efficacious as monotherapy or in conjunction with insulin (15), metformin (16), or sulfonylureas (17). Nevertheless, monotherapy with troglitazone is discouraged because of hepatotoxicity, which is lower with rosiglitazone and pioglitazone. The effect of thiazolidinediones in preventing coronary artery disease requires further study, but positive data has emerged from a randomized, controlled trial showing troglitazone reducing neointimal hyperplasia (a cause of stent restenosis) in diabetics receiving coronary stents (Table 1) (18).

Sulfonylureas target pancreatic beta cells, where they block potassium-adenosine triphosphate (K-ATP) channels, thereby increasing intracellular calcium and promoting the release of insulin. This method controls blood sugar but is worrisome, since it may induce hypoglycemia in patients. The UKPDS data revealed a 16% reduction in myocardial infarctions (MI) for patients treated with sulfonylurea or insulin, with no significant difference between the two agents. There was a 1 – 1.4% yearly rate of severe hypoglycemia in the sulfonylurea-treated group (7).

An additional concern emerges from trials showing an increased risk of MI and death in the setting of ischemia for patients taking sulfonylureas. The blocking of cardiac K-ATP channels is purported to reduce ischemic preconditioning, a phenomenon in which the heart becomes tolerant to further ischemia or reperfusion after an initial ischemic insult (19). This claim has been supported in a study showing increased in-hospi-

TABLE 1

IVUS Were Performed on 62 Stented Lesions in 52 Patients with NIDDM to Determine Whether Troglitazone (400 mg) Reduced Neointimal Tissue Proliferation after Coronary Stent Implantation*

IVUS Measurements after 6 months of treatment	Troglitazone (n=29 stents)	Control (n=33 stents)	p value
Stent area (mm^2)	7.3±1.8	7.3±2.3	0.7995
Lumen area (mm^2)	5.3±1.7	3.7±1.7	0.0002
Intimal area (mm^2)	2.0±0.9	3.5±1.8	<0.0001
Intimal index (%)	27.1±11.5	49.0±14.4	<0.0001

Reprinted with permission from J Am Coll Cardiol 2000; 36(5):1529–1535, Table 3 (18).

*IVUS = quantitative intravascular ultrasound studies
NIDDM = non-insulin-dependent diabetes mellitus.

$$\text{Intimal Index} = \frac{\text{Averaged Intimal Area}}{\text{Averaged Stent Area}} \times 100\%$$

Reduction in plasma glucose and insulin levels was significantly greater with troglitazone as compared to placebo ($p<0.0001$ for both).

tal mortality of diabetics taking sulfonylureas and receiving percutaneous transluminal coronary angioplasty (PTCA) for acute MI. However, long-term mortality, risk of MI and need for coronary artery bypass graft (CABG) were no different between the two groups (20). This potential harm has also been disputed by the UKPDS data, which demonstrated no difference in myocardial events between the sulfonylurea group and the insulin group. Further study is necessary to resolve this issue.

Metformin promotes glucose control in two ways: (a) by decreasing hepatic glucose release through an inhibition of gluconeogenesis, and (b) by increasing the sensitivity of peripheral tissue to insulin (21). In the UKPDS trial, metformin demonstrated significant reductions in all diabetes-related endpoints for obese diabetics. This finding, combined with its effect on promoting weight loss and reduced risk of hypoglycemia, supports metformin as a first line therapy, particularly for obese patients (22). Metformin also improves lipid and coagulation profiles. Decreased levels of LDL, triglycerides and plasminogen activator inhibitor-1 (PAI-1), which have been observed in treatment groups, may provide additional protection from cardiovascular disease (23). Lactic acidosis is a side effect, although rare, and limits the use of metformin in patients with chronic renal insufficiency, congestive heart failure, or hypoxia (24).

Hyperlipidemia

Dyslipidemia in diabetics involves elevated triglyceride levels and decreased HDL levels. While LDL is typically normal in type 2 diabetics, it is often small and dense, with impaired antioxidant defenses. Glycosylation of protein and phospholipid components further increases its vulnerability to oxidative changes, a process that promotes atherogenesis (25).

Elevations of very low-density lipoproteins (VLDLs) are also seen. These VLDLs are the result of: (a) increased free fatty acid return to the liver due to obesity, which increases available quantities of fatty acids, and (b) insulin resistance, which decreases catabolism of fatty acids by peripheral tissue. In the liver, these fatty acids are used to generate triglyceride-rich VLDLs of varying sizes, which are atherogenic. Lipoprotein lipase, an enzyme responsible for eliminating VLDL within the circulation, is less active in diabetics, further contributing to VLDL increase (26).

Elevated VLDL is also involved in the pathogenesis of decreased HDL levels. With their triglyceride-rich cores, VLDLs promote the exchange of triglycerides for key cholesterol components in HDL, resulting in a triglyceride-laden HDL that is easily degraded by enzymes (27). Moreover, studies have shown that the circulating HDL in diabetic patients may be less effective in preventing coronary artery disease (CAD), by allowing the oxidation of LDL to occur unchecked (28). Altogether, these triglyceride-mediated changes in VLDL and HDL may account for hypertriglyceridemia as a risk factor for coronary disease in diabetics, but not in the general population.

Multiple trials have demonstrated benefits from treatment with hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (simva-

TABLE 2

A Series of Clinical Trials Demonstrating the Risk Reduction of Major Coronary Events for Patients Treated with HMG-CoA Reductase Inhibitors (29–34)

Study	Drug	No. of Diabetics	Risk Reduction (nondiabetics)	Risk Reduction (diabetics)
Primary Prevention				
AFCAPS/TexCAPS	lovastatin	239	37% (all patients)	43%
Secondary Prevention				
Heart Protection Study	simvastatin	5963	27% (all patients)	27% * (p<0.0001)
CARE	pravastatin	586	23%	25% (p=0.05)
4S	simvastatin	202	32%	55% (p=0.002)
LIPID	pravastatin	782	25%	19%
4S-extended	simvastatin	483	32%	42% (p=0.001)

* A portion had no prior cardiovascular disease, thereby providing data for primary prevention.

statin, pravastatin) and fibric acid derivatives (gemfibrozil) as modes of lipid therapy. Subset analyses from these data show similarities in cardiovascular risk reduction for diabetics, compared to nondiabetics (Table 2) (29–34). The 4S and CARE trials yielded significant declines in the rates of death, nonfatal MI, and revascularization in diabetics treated with simvastatin and pravastatin, respectively, against placebo. The latter trial showed a 25% reduction in cardiac events over 5 years. Gemfibrozil is effective in raising HDL levels and lowering triglycerides, both of which are effective in limiting the progression of heart disease. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a 22% reduction in cardiac deaths and nonfatal MIs combined was observed among diabetics treated with gemfibrozil against placebo. LDL levels were normal and unaffected during the treatment period (35). Similar benefits were seen years earlier in the Helsinki Heart Trial, indicating the importance of treating low HDL, even with normal LDL, as is seen in many type 2 diabetics (36).

Hypertension

The presence of hypertension in diabetic patients significantly increases their risk of micro- and macrovascular complications, including retinopathy, nephropathy and cardiac disease. Several studies have demonstrated the benefits of blood pressure control in reducing these morbid sequelae. In the UKPDS trial, a target blood pressure of <150/85 resulted in a 24% risk reduction in diabetes-related endpoints (p=0.0046), including a 34% risk reduction (p=0.019) in combined macrovascular disease (MI, sudden death, stroke, and peripheral vascular disease) and a 37% reduction in risk of microvascular disease (p=0.0092). The 21% reduction in MI was not statistically significant, but the risk of heart failure decreased by 56% (p=0.0043) (37).

In the UKPDS trial, these results were similar whether blood pressure was controlled with a beta-blocker (atenolol) or with an angiotensin-converting enzyme (ACE)-inhibitor (captopril), suggesting no advantage between different blood pressure regimens (38). However, recent data dispute this finding. The Captopril Prevention Project (CAPPP) trial demonstrated a statistically significant decrease in cardiac events, including MI and cardiovascular mortality, in diabetic patients treated with captopril vs. beta-blocker and diuretic therapy (39). Additionally, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial showed fewer episodes of fatal and nonfatal MIs in diabetics taking enalapril vs. a calcium channel blocker (nisoldipine) (40).

For diabetics, ACE-inhibitors may exert cardiovascular protection beyond their blood pressure lowering effect. This was seen in the Heart Outcomes Prevention Evaluation (HOPE) trial, where 5-year rates of MI, stroke, and cardiovascular mortality were reduced in diabetics treated with enalapril compared to placebo (relative risk reduction=25%, p=0.0004). This benefit was disproportionately larger than the mean drop in systolic blood pressure (6 mm Hg). Since many of these patients also did not have baseline hypertension, enalapril may be cardioprotective through other mechanisms, possibly related to angiotensin II blockade. These are thought to include reduced vasoconstriction and left ventricular hypertrophy, improved endothelial function, decreased smooth muscle proliferation, and stabilization of coronary plaques (41).

The concept of further lowering blood pressure, even when patients are "normotensive," appears particularly beneficial in diabetics. The Hypertension Optimal Treatment (HOT) study yielded a 50% reduction in major cardiovascular events in diabetic patients with diastolic blood pressures of 80 mm Hg or less compared to pressures of 90 mm Hg or less. A similar improvement was seen for strokes, silent MIs, and cardiovascular mortality (42).

Beta-blocker treatment for diabetics has traditionally focused on post-MI patients, for whom mortality benefits have been proven (43). Yet there are concerns that these agents may be harmful to diabetics by masking hypoglycemic symptoms, raising lipid levels and worsening glucose tolerance. Recent data show no long-term effects on lipid profiles, although lower HDL levels and higher triglycerides were seen during the initial titration period (44). Furthermore, studies of MI patients treated with beta-blockers show no increase in complications related to their diabetes (45). Meanwhile, the benefits of treatment have become increasingly apparent. The Benzafibrate Infarction Prevention (BIP) study showed a 42% reduction in cardiac mortality in type 2 diabetics treated with beta-blockers. These patients had chronic CAD and remote histories of MI, suggesting a broader role for therapy beyond the immediate post-MI period (46).

Antiplatelet Drugs

Elevated levels of thromboxane, fibrinogen, PAI-1 and several coagulation factors suggest a link between diabetes and a procoagulant state (47). Antiplatelet therapy involves multiple pharmacologic agents, each with its own mechanism for platelet inhibition. The three major drugs used in cardiovascular disease include aspirin, clopidogrel and intravenous glycoprotein (GP) IIb/IIIa inhibitors.

Data from the BIP study suggest that diabetics derive even greater cardiovascular benefits from aspirin than do nondiabetics (48). One reason may have to do with elevated levels of thromboxane, a platelet aggregant, observed in diabetics and inhibited by aspirin therapy. For this reason, low-dose aspirin therapy is recommended as a primary prevention in diabetics with one other risk factor for coronary disease (49).

The role of additional antiplatelet agents is important for diabetics, since they experience increased mortality from acute coronary syndromes (ACS) (50). Clopidogrel (Plavix) blocks adenosine diphosphate-mediated platelet activation and subsequent aggregation. Its efficacy in acute coronary syndromes was demonstrated in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, in which patients treated with aspirin plus clopidogrel, compared to aspirin alone, had significant risk reductions in cardiovascular mortality, nonfatal MI and stroke combined, as well as refractory ischemia (51). An extension of this effect was seen in patients receiving long-term clopidogrel therapy after percutaneous coronary intervention (PCI) (Fig. 2) (52). Necessity for target vessel revascularization within 30 days of PCI was also significantly less in the treated group (53). In both studies, diabetic subgroups also demonstrated these benefits.

Intravenous GPIIb/IIIa inhibitors target the final step in platelet aggregation, where fibrinogen binds glycoprotein IIb/IIIa and promotes cross-linking of platelet molecules (53). The PRISM-PLUS study showed decreased mortality, myocardial infarction and refractory ischemia after 7 days in diabetics with unstable angina treated with a GPIIb/IIIa plus heparin vs. heparin alone (54). A meta-analysis of six GPIIb/IIIa trials, including PRISM-PLUS, demonstrated a 30-day mortality reduction from 6.2% to 4.6% (p=0.007) in diabetics with ACS and an even greater benefit in diabetics undergoing PCI. No survival difference was seen between therapies for nondiabetics (55).

Myocardial Infarction

Management of acute MI in diabetics is of special concern, since they have a higher incidence and a higher mortality from these events.

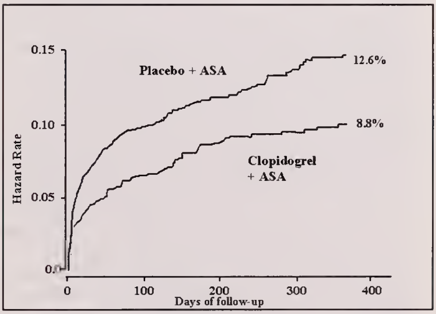

Fig. 2. Long-term clopidogrel therapy in 2,658 patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention showed a 31% risk reduction in cardiovascular death and myocardial infarction (p=0.002). ASA = aspirin. Reprinted with permission from Elsevier, Lancet 2001; 358:527–533 (52).

Thrombolytic therapy has the same, if not greater short-term benefits for diabetics vs. nondiabetics in spite of their elevated coagulation factors. Multiple angiographic studies have demonstrated similar patency rates between these two groups 90 minutes after thrombolysis (56). And an analysis of all thrombolytic trials demonstrated a non-significant, but increased 35-day survival rate for diabetics (57).

Novel approaches for improving survival after myocardial infarction include aggressive glucose control with insulin during the peri-infarct period. The DIGAMI trial randomized diabetic patients with acute MIs to insulin infusion for 24 hours upon hospitalization, followed by three months of subcutaneous insulin therapy. This was compared to standard glucose control therapy. A 30% and 28% reduction in mortality was seen in the insulin infusion group after 1 and 3.4 years of follow-up, respectively (58).

Revascularization

Coronary revascularization, through angioplasty or CABG, is critical to any long-term survival strategy for patients with cardiovascular disease. Diabetes poses a unique challenge by accelerating the development of multi-vessel atherosclerosis before and after these procedures (59). The effect this has on the management of diabetics is seen in results from the Bypass Angioplasty Revascularization Investigation (BARI) trial. This study demonstrated that 5-year survival rates were significantly improved for diabetics with multi-vessel disease treated with CABG (survival rate 80.6%) compared to balloon angioplasty (65.5% survival, p=0.003). This difference was not seen in the nondiabetic subset. The benefits of surgery could be explained by more widespread coronary disease in diabetics, and higher rates of restenosis after PTCA (60). Interestingly, other trials do not confirm this result. A prospective nonrandomized study at Duke University found no difference in 5-year survival between diabetics with multi-vessel disease treated with CABG compared to PTCA (61). Furthermore, an examination of outcomes among BARI registry patients yielded similar 7-year mortality rates (26%) between CABG and PTCA-treated diabetics when physicians chose the modality of revascularization, selecting PACA for 65% of all patients (62). Regardless of the therapy, diabetics still demonstrate higher mortality rates than nondiabetics after PCI, resulting in large part from higher rates of restenosis.

The problem of restenosis is being addressed through advances in PCI techniques, including antiplatelet administration and coronary stent placement. The EPIC and EPILOG trials demonstrated a reduction in acute ischemic complications after angioplasty with the administration of a GPIIb/IIIa inhibitor (63). The latter trial showed a continuation of benefits six months after therapy (64).

Furthermore, placement of coronary stents during angioplasty significantly lowers restenosis rates in simple lesions for both diabetics and nondiabetics, as demonstrated by the STRESS and BENESTENT trials (65). The BENESTENT study showed a 22% restenosis rate after stent insertion compared to 32% for angioplasty alone (p=0.02), with benefits also seen after 5-year follow-up (66, 67).

A combination of stent and antiplatelet therapy demonstrates the most significant mortality benefits. The EPISTENT trial compared outcomes after 6 months for patients treated with stent combined with abciximab (GPIIb/IIIa inhibitor), abciximab and angioplasty, or stent placement alone. There was a 50% reduction in mortality, nonfatal MI and repeat revascularization for diabetics receiving stent and abciximab vs. stent and placebo. Diabetics also showed lower rates of repeat target vessel revascularization after treatment with stent and abciximab (8.1%) vs. angioplasty and abciximab (18.4%, p=0.008) or stent alone (16.6%, p=0.02) (68).

Even with the advent of coronary stents, CABG appears to be more beneficial in diabetics compared to PCI. In the Arterial Revascularization Therapy Study (ARTS) trial, diabetics receiving CABG surgery had significantly fewer cardiac events (84.4% event-free survival) at one year than those treated with multi-vessel stenting (63.4% event-free survival, p<0.001). One reason was the greater need for repeat revascularization procedures in the PCI group due to stent restenosis. The addition of a GPIIb/IIIa inhibitor may improve outcomes for diabetics receiving multi-vessel stenting, but this requires further study (69).

Preventing stent restenosis is the current challenge in coronary revascularization. Restenosis, which is accelerated in diabetics, results from neointimal hyperplasia secondary to smooth muscle proliferation. Many oncologic agents are being studied for their effect on inhibiting this process, including paclitaxel, c-myc, sirolimus, actinomycin-D, tacrolimus and dexamethasone. For example, sirolimus binds to its intracellular receptor protein $FKBP_{12}$ in target

TABLE 3

Angiographic and Clinical Data for Diabetic Subsets in Two Trials Testing Sirolimus-Eluting Stents (70, 71)

	Sirolimus	Control	p Value
RAVEL	n=19	n=25	
Late luminal loss (mm)	0.07	0.82	<0.001
Cardiac events (%) (at 12 months, all patients)	5.8	28.8	<0.001
SIRIUS	n=131	n=148	
In-segment restenosis (%)	17.6	50.5	<0.001
Target lesion revascularization (%)	6.9	22.3	<0.001

"Late luminal loss" denotes the difference between minimal lumen diameter immediately after procedure and at six months.

cells, resulting in elevations of p^{27kip1}, a cyclin-dependent kinase inhibitor. This reduces phosphorylation of cell-cycle progression protein Rb (retinoblastoma protein), thereby inducing cell cycle arrest and inhibition of vascular smooth muscle proliferation (53). These drugs, however, have shown little success when given systemically, leading to the development of *in-situ* delivery systems such as drug-eluting stents. Local administration of these drugs allows higher doses to be given with less concern for the toxic side effects associated with systemic delivery. Favorable results have been achieved in clinical trials using sirolimus-eluting stents for patients with and without diabetes (Table 3). Results of the RAVEL trial demonstrated significantly reduced rates of neointimal hyperplasia in patients treated with sirolimus-coated stents versus non-coated stents. This resulted in a reduction of stent restenosis at six months with no patients showing greater than 50% stent narrowing in the sirolimus group compared to 25% ($p<0.001$) in the standard group. Diabetics in this study experienced similar benefits, showing 0% restenosis with sirolimus but 41.7% restenosis without the drug ($p=0.002$) (70).

The SIRIUS trial randomized 1,058 patients (279 diabetics) to sirolimus-coated stents vs. standard stents, and followed clinical endpoints at 9 months. Diabetics showed statistically significant reductions in the rates of restenosis and repeat revascularization (Table 3) in addition to decreased MI and death (71). The FREEDOM Trial will investigate whether drug-eluting stents can improve outcomes in diabetics with multi-vessel disease when compared to CABG.

Future Directions

Diabetes poses a unique and pressing challenge in the management of cardiovascular disease. The BARI-2D trial will address many unanswered questions in this area, including the role of revascularization in stable, and even asymptomatic, CAD in diabetics. Patients will be randomized to aggressive medical management combined with revascularization (CABG or PCI) vs. aggressive medical management only. The study will also examine outcome differences between an insulin-based approach to glycemic control and an insulin-sensitizing strategy, which targets insulin resistance (72). In the future, the clinical effects of new pharmacologic agents, such as the thiazolidinediones, in preventing development and progression of cardiovascular disease will need to be addressed. Moreover, the potential negative impact of current pharmacologic agents in diabetics, such as sulfonylurea in acute myocardial infarctions, requires further study. And with the advent of drug-eluting stents, many of the same management questions and dilemmas addressed in prior clinical trials with diabetics will be revisited.

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Familial Polyposis Coli:

Clinical Manifestations, Evaluation, Management and Treatment

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Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant, hereditary colon cancer syndrome that is characterized by the presence of innumerable adenomatous polyps in the colon and rectum. Gardner's syndrome is a variant of FAP, which in addition to the colonic polyps, also presents extracolonic manifestations, including desmoid tumors, osteomas, epidermoid cysts, various soft tissue tumors, and a predisposition to thyroid and periampullary cancers. Mutations of the *APC* gene are thought to be responsible for the development of FAP, and the location of the mutation on the gene is thought to influence the nature of the extracolonic manifestations that a given patient might develop. Though patients are often asymptomatic, bleeding, diarrhea, abdominal pain and mucous discharge frequently occur. Diagnostic tools include genetic testing, endoscopy, and monitoring for extra-intestinal manifestations. Currently, surgery is the only effective means of preventing progression to colorectal carcinoma. Restorative proctocolectomy with ileal pouch anal anastomosis (RPC/IPAA) with mucosectomy is the preferred surgical procedure, since it attempts to eliminate all colorectal mucosa without the need for an ostomy. Periampullary carcinoma and intra-abdominal desmoid tumors are a significant cause of morbidity and mortality in these patients after colectomy. Frequent endoscopy is needed to prevent the former, while there is no definitive treatment available yet for the latter. The following article presents a case and reviews the evaluation, management and treatment of Gardner's syndrome.

Key Words: Gardner, familial adenomatous polyposis, hereditary colon cancer, desmoid tumors.

Case Report

THE PATIENT WAS A 39-YEAR-OLD FEMALE with a two-month history of intermittent rectal bleeding. She reported no symptoms of weight loss, anorexia, or abdominal pain. Her family history included several individuals on her mother's side (maternal uncle and several cousins) with colon cancer during their third and fourth decades of life. The patient had been told that they had "Gardner's syndrome," but she was unaware that she was also at risk. The patient was afebrile with normal vital signs. Her abdomen was soft, nontender and nondistended, and had hypoactive bowel sounds. Her rectal examination was negative. Her complete blood count (CBC) was significant for anemia, with a hematocrit of 28. On colonoscopy, she was found to have numerous polyps carpeting the entire colon and rectum, which was consistent with familial adenomatous polyposis (FAP). An upper endoscopy was negative. A CT scan did not reveal any desmoid tumors, and a small bowel series revealed no abnormalities. She underwent a restorative proctocolectomy with mucosectomy and ileal-pouch/anal anastomosis. Pathology of the specimen confirmed the diagnosis of familial adenomatous polyposis (Figs. 1 and 2). There was no evidence of cancer. On discharge, it was recommended that all family members be evaluated for FAP.

Introduction

Each year, approximately 148,300 individuals are diagnosed with colon cancer; 56,500 cases will result in death (1). Nearly 5 – 10% of colon cancers are autosomal dominant and follow a Mendelian pattern of inheritance. The two major forms of hereditary colon cancer are hereditary nonpolyposis colorectal cancer (HNPCC) and FAP. The following discussion will briefly review FAP and focus on Gardner's syndrome, a variant of FAP with characteristic extracolonic manifestations.

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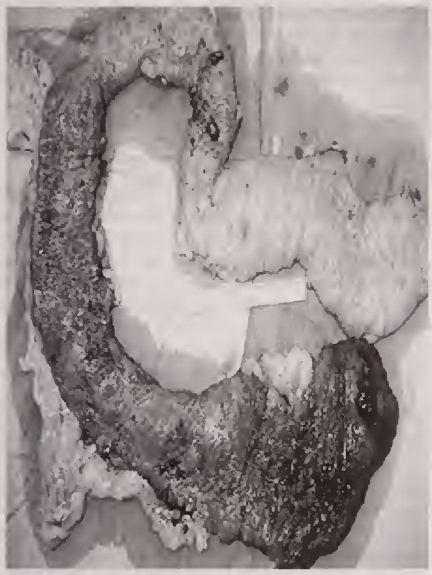

Fig. 1. The entire colectomy specimen. From a distance, the left colon appears to be less involved than the right side.

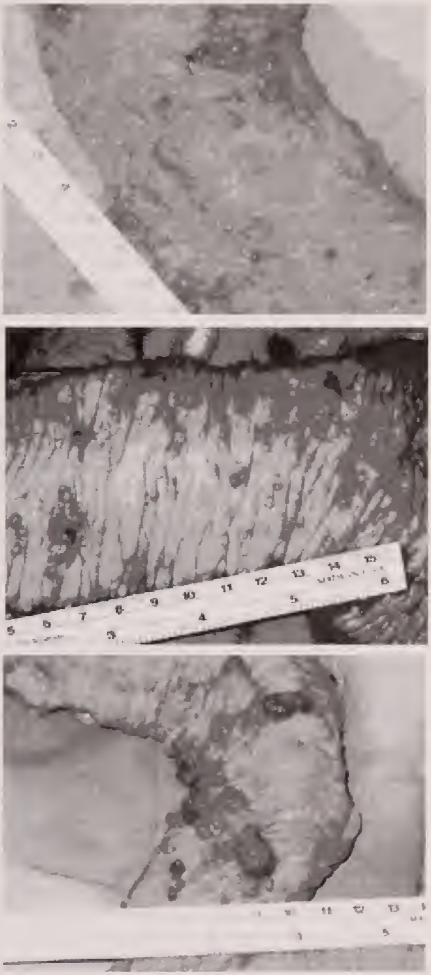

Fig. 2. Close-up view of the mucosal aspect of the sigmoid colon, showing numerous adenomatous polyps throughout.

FAP

FAP is an autosomal dominant disease of the colon characterized by the presence of innumerable adenomatous polyps. The incidence of this disorder is between 1 in 8,300 and 1 in 14,025 live births, affecting both genders equally, with a uniform worldwide distribution (2). Without colectomy, the development of colorectal cancer is inevitable and is thought to occur approximately 10–15 years after the onset of polyposis (3, 4). The average age at diagnosis is 34.5–43 years and the average age at diagnosis of colorectal cancer is 39 years (3–5). The genetic defect in FAP has been linked to germline mutations of the *APC* gene on chromosome 5q21 (6). *APC* is a tumor-suppressor gene and has a putative role in cell adhesion, signal transduction and transcriptional activation (7).

Patients are usually asymptomatic prior to the appearance of polyps, which start to develop at puberty. Polyposis continues into adulthood until the entire colon is carpeted with adenomas. The histology of polyps seen in FAP is similar to that of sporadic polyps and displays tubular, villous and tubulovillous characteristics. The cancer risk is thought to be a function of the number of the polyps found in the colon (8). On average, 1000 macroscopic polyps are noted to be present on diseased specimens, with tens of thousands of polyps less than 1 cm in diameter (Figs. 1 and 2).

Genetics

The gene responsible for FAP, the *APC* gene, is a large gene with more than 1400 different reported mutations (9–11). The mutated *APC* allele is inherited as a germline mutation from the affected parent. Interestingly, however, adenomas develop only when the second allele (inherited from the unaffected parent) mutates or is inactivated (12). The pathway controlled by the *APC* gene includes *c-myc* and *beta-Catenin* as downstream targets and appears to impact kinetochore and microtubule attachment.

The APC protein is a multifunctional regulator of colonic epithelial cell renewal. In addition to its role as a tumor suppressor protein, it regulates cellular proliferation, differentiation, migration and apoptosis. Mutations in *APC* interfere with the way epithelial cells divide and distribute their nuclear DNA (13). Since most *APC* mutations result in deletions of the carboxy terminal, this domain is considered to carry the tumor suppressor function (14).

In FAP, a clear correlation between the specific clinical features and the location of the mutation on the *APC* gene (termed the genotype-phenotype correlation) has been observed (15). For example, an increased risk of desmoid tumors is associated with mutations between codons 1445 and 1578. Similar correlations have been made between congenital hypertrophy of pigmented retinal epithelium and attenuated FAP (16, 17). These correlations are not yet uniform, and their current value lies in their ability to direct screening and diagnostic testing.

Prior to identification of the *APC* gene, a number of variants of FAP had been described, based on different extracolonic manifestations. With the information we currently have, it is believed that many of these syndromes merely reflect the variety of locations of mutations on the *APC* gene. These syndromes include Gardner's syndrome (multiple osteomata, cysts and soft tissue tumors), Turcot's syndrome (FAP in association with malignant tumors of the central nervous system), Cronkhite-Canada syndrome (gastrointestinal polyposis, skin hyperpigmentation, alopecia and nail dystrophy), and attenuated FAP or AFAP (<100 colonic adenomas with right-sided predominance) (18, 19).

Gardner's Syndrome

When FAP is associated with desmoid tumors, mesenteric fibromatosis, dental abnormalities, gastric polyps, duodenal polyps, lymphoid hyperplasia of the terminal ileum and ileal adenomas, it is called Gardner's (or Gardner) syndrome. The syndrome, first described in 1951, was initially thought to be an entity of its own (20).

Clinical Manifestations

The most common symptoms related to the polyposis are bleeding, diarrhea, abdominal pain and mucous discharge. Weight loss, anemia and intestinal obstruction imply the presence of cancer, and an estimated 25% of patients with the syndrome have colorectal cancer at diagnosis (21).

An often-lethal complication of FAP is diffuse mesenteric fibrosis or desmoid tumors. Their reported incidence among patients with Gardner's syndrome is 3.5–5.7% and they commonly manifest 1–3 years following surgery (22, 23). These neoplasms usually arise in abdominal incisions, the abdominal cavity or the retroperitoneum (24, 25). Some authors regard desmoid tumors as the most troubling consequence of Gardner's syndrome. Extensive small bowel resection secondary to obstruction and urinary obstruction are common complications of desmoid tumors. Death is usually secondary to intestinal obstruction or vascular occlusion (26, 27). Among patients with FAP, desmoid tumors have a high recurrence rate and are only resected when symptomatic. In a series reported by Jones et al., 50% of patients had complications (intestinal obstruction, hydronephrosis and fistulas) and 2 of the 9 deaths were attributed to desmoid tumors (27). Since desmoid tumors are a common cause of morbidity and mortality in this population, various treatment options have been investigated (see "Management of Desmoid Tumors," below).

Since the *APC* gene is a germline mutation, tumors develop in various extracolonic sites, including thyroid and adrenal glands, liver, duodenum and pancreas (28–31). Periampullary carcinoma (carcinoma of the duodenum, ampulla of Vater or pancreas) has been strongly associated with Gardner's syndrome. Research at St. Mark's Hospital, London, indicated a 12% incidence of periampullary cancer in a series of patients 5 years after colectomy (22). Similar associations have been reported by Sugihara (32). It is strongly recommended that patients with Gardner's syndrome or FAP undergo frequent upper gastrointestinal endoscopy and radiological studies looking for abnormalities in these other extracolonic sites.

Epidermoid cysts are common benign findings in the general population and are thought to occur more frequently among patients with Gardner's syndrome. Since they are usually uncommon prior to puberty, their presence prior to puberty should alert the physician to evaluate the colon and the rectum for polyps (22, 33).

Osteomas in relation to Gardner's syndrome are typically found in the skull and mandible, and might be the only extracolonic manifestation related to the disease (34, 35).

Asymptomatic pigmented ocular fundic lesions are present in more than 90% of patients with FAP or Gardner's syndrome (36). It has been suggested that the presence of congenital hypertrophy of the retinal pigment epithelium, if demonstrated in relatives, is almost 100% predictive of FAP (37).

The Table lists some of the extracolonic symptoms that have been described in association with FAP (18, 19).

Evaluation

As in any disease with a strong genetic component, an extensive family history is useful in establishing the diagnosis. A combination of endoscopy, genetic testing and observation of extracolonic manifestations is used in the diagnosis of FAP and Gardner's syndrome.

Genetic testing is the most efficient mode of identifying gene carriers in a FAP relative. In cases where the exact sequence of a mutation is known in one family member, direct sequencing directed at the region of the *APC* gene thought to be affected has been shown to be 90% cost effective and accurate (38). Linkage analysis to markers on chromosome 5q, protein truncation testing, direct sequencing, conformation-sensitive gel electrophoresis, and single-strand, conformation-sensitive gel electrophoresis all have accuracies between 70% and 90% (39).

Screening colonoscopy should begin at age 10 – 12 years for patients who are known to have *APC* mutations (19). Individuals who are at risk with an unknown mutation status should have screening colonoscopies by age 15, every year from age 26 – 35, every other year from age 26 – 35, and every three years from age 36 – 50.

Although there are no clear guidelines for upper endoscopy, all patients should have forward-viewing extended and side-viewing upper tract endoscopies (40 – 42). Duodenal polyps > 0.5 – 1 cm should be removed and the follow-up interval should be based on the histology of the polyp. Polyps that are villous or harbor high-grade dysplasia should have follow-ups every 2 – 3 months until ablation is achieved. When polyps carpet the mucosa or when complete ablation is not achieved endoscopically, surgical intervention is required. Ampullary polyps > 2 cm should be removed with surgical resection (41, 42).

An annual physical examination to screen for thyroid cancer is warranted. Liver ultrasonography and serum alpha-fetoprotein are being investigated as possible screening tests for hepatoblastoma.

Medical Management

The chemopreventive drugs used most extensively for patients with FAP have been the cyclo-oxygenase inhibitors. Some studies have reported a regression of polyps and biochemical markers after the use of these agents. However, primary chemoprevention of colorectal adenomas was not achieved in FAP patients treated with sulindac (43, 44). The use of cyclo-oxygenase inhibitors in conjunction with ursodeoxycholic acid is being studied for its effect on duodenal polyps, ileal pouch polyps, and desmoids. Vitamin C, vitamin E, and supplemental wheat fiber have not had a clinically sig-

TABLE

Benign and Malignant Lesions Associated with Familial Adenomatous Polyposis

Malignant Tumors (lifetime risk)	Other Lesions
Duodenal (5 – 11%)	Nasopharyngeal angiofibromas
Pancreatic (2%)	Osteomas
Thyroid (2%)	Radiopaque jaw lesions
Brain (medulloblastoma) <1%	Supernumerary teeth
Hepatoblastoma (0.7% of children < 5yrs)	Lipomas, fibromas, epidermoid cysts
	Desmoid tumors
	Gastric adenomas/fundic gland polyps
	Duodenal, jejunal and ileal adenomas

nificant impact on the appearance or progression of polyps (12).

Surgical Management

Surgery is the only effective therapeutic option currently available to prevent progression to colorectal cancer. The chief considerations are the timing and the extent of surgery. The general recommendation is that prophylactic colectomy should be performed by the late teens in patients for whom the diagnosis of FAP is made.

The current surgical options include the following:

1. Total proctocolectomy (TPC) with ileostomy.
2. Restorative proctocolectomy with ileal pouch anal anastomosis (RPC/IPAA) with mucosectomy.
3. RPC/IPAA using double staple technique.
4. Total abdominal colectomy with ileorectal anastomosis (IRA) with rigorous surveillance of the rectal remnant.

TPC with ileostomy carries the disadvantage of a permanent ileostomy, which can be a severe drawback to a young patient in his/her teens. This procedure is only done when a proctocolectomy is required and there is a contraindication to performing an IPAA.

Options 1 and 2 are preferred because they attempt to eliminate all colon and rectal mucosa, thereby assuring that these patients have the lowest risk of developing colorectal cancer. An RPC/IPAA with mucosectomy restores bowel continuity and attempts to eliminate all rectal tissue and subsequent cancer risk. The disadvantage of RPC/IPAA with mucosectomy is that this operation is reported by some authors to be technically more difficult (45, 46). TPC with ileal pouch-anal anastomosis, including mucosectomy to the dentate line, has been the preferred approach at the Mayo Clinic. They have reported a low postoperative complication risk and satisfactory functional results of the ileal pouch (36, 47 – 49).

Some authors suggest that islands of rectal mucosa might be retained, even with mucosectomy. Reports have indicated that the risk of dysplasia and polyp formation is decreased but not eliminated (50 – 52). The Cleveland Clinic group reported that a stapled anastomosis offers a better functional outcome and might prevent the need for a diversion. However, they recommend that this superior outcome should be balanced against a 28% increase in the incidence of adenomas in the anal transitional zone (51). If a transitional zone neoplasia is found on surveillance after a stapled anastomosis, the transitional zone can be stripped transanally and the pouch advanced to the dentate line (53).

Experience with total abdominal colectomy with IRA is largely from the Cleveland Clinic and St. Marks groups (54, 55). The Cleveland Clinic protocol included colectomy by age 20, anastomosis at 12 cm from the dentate line, and follow-up every 6 months. Some authors have argued that colectomy might lead to the spontaneous regression of polyps, but the permanence of this regression is questionable (56 – 59). Of a group of 89 patients studied by the Mayo group, two developed rectal cancer. However, since the center adhered to rigorous follow-up care, the cancers were identified at an early stage (36). It is argued that the risk of rectal cancer is related to the number of polyps. IRA might therefore be an appropriate choice for patients with attenuated FAP or relative rectal sparing (<20 rectal adenomas, 1,000 colonic adenomas) (50).

The surgical options must be tailored to the needs of the individual patients and their reliability to maintain follow-up care. A review of 115 patients with FAP at Mount Sinai Medical Center revealed that one out of four patients with ileorectal anastomosis developed rectal cancer at a mean follow-up time of 13 years (60). This study also suggested that rectal cancer in these populations tends to be advanced tumors. Therefore, excision of the entire colorectal mucosa is considered to be the treatment of choice. Similar recommendations have been reported at other institutions (61 – 63).

In light of these factors, the preferred procedure for most patients with FAP is an RPC/IPAA with mucosectomy. Moreover, any surgical procedure that restores intestinal continuity must be followed up with rigorous surveillance. A mucosectomy does not eliminate the risk of malignancy and should by no means offer a false sense of security.

The development of adenomas within the ileal pouch several years after the surgery is a well-recognized phenomenon. However, the natural history of ileal adenomas and their risk for progression to cancer is incompletely characterized (36).

Management of Desmoid Tumors

Since desmoid tumors are a cause of significant morbidity and mortality in this population, the management of desmoid tumors requires special attention. A strong family history of desmoid tumors and a high-risk location of the mutation on the *APC* gene increase the risk for the development of desmoid tumors. Due to a reported 85% recurrence rate of desmoid tumors after surgical excision, surgery should be performed only when absolutely necessary. Some reports have suggested that abdominal wall desmoids respond more favorably to surgical resection because they are often encapsulated (64–66). The presence of desmoid tumors might favor an IPAA over an IRA, because IRA might require additional surgery in the future.

Tamoxifen, toremifene, and sulindac have been used as treatments, but the results have not been promising. Reports have suggested that therapy might be associated with an initial benefit but the long-term clinical improvement is minimal (65–71). Cytotoxic chemotherapy (doxorubicin, dacarbazine, and carboplatin) may be effective in treating aggressive, rapidly growing and unresectable intra-abdominal desmoids. Significant side effects include febrile neutropenia, nausea, vomiting, stomatitis, thrombocytopenia and epistaxis (72, 73). Radiation therapy might be effective in some cases but frequently carries complications (74).

Intra-abdominal desmoid tumors usually involve the mesentery and often involve the mesenteric vessels. They invade the mesentery diffusely, kink loops of bowel and can obstruct the ureters. Large and complex resections are required and recurrence is very common. Surgery is usually reserved as a last resort for intra-abdominal desmoids. The presence of desmoids might prevent the construction of a pouch and might require the creation of a permanent ileostomy (75–77). The management of intra-abdominal desmoid tumors is complex and is dependant on their clinical behavior. Based on the American Society of Colon and Rectal Surgeons Guidelines, slow-growing and inert intra-abdominal desmoids should be treated with sulindac or not treated at all. Desmoids that are growing slowly or are mildly symptomatic can be treated with sulindac and tamoxifen or with vinblastine and methotrexate, since these regimens are less toxic. Aggressive desmoids are treated with antisarcoma chemotherapy such as doxorubicin and dacarbazine. Intestinal transplant has been attempted to rescue FAP patients with desmoid tumors (78).

Surgical therapy is favored for abdominal wall desmoid tumors, since they are easier to excise than intra-abdominal desmoid tumors, recurrence rates are lower, and morbidity associated with the procedure is less. The excision should be completed with a 1 cm margin. A mesh can be used to cover the defect if required (50).

Conclusion

FAP is an autosomal dominant, hereditary colon cancer syndrome that is characterized by the presence of innumerable polyps in the colon and rectum. Gardner's syndrome is a variant of FAP characterized by extracolonic manifestations, including desmoid tumors, osteomas, epidermoid cysts, various soft tissue tumors, and a predisposition for thyroid and periampullary cancers. Diagnostic tools include genetic testing, endoscopy, and monitoring for extra-intestinal manifestations. Currently, surgery is the only effective means of preventing progression to colorectal carcinoma. RPC/IPAA with mucosectomy is the preferred surgical procedure for these patients, as it attempts to eliminate all colorectal mucosa. In addition, aggressive surveillance is required to decrease the morbidity and mortality from the various extracolonic manifestations. Periampullary carcinomas and desmoid tumors are significant causes of morbidity and mortality in these patients. Frequent endoscopy is needed to prevent the former, while there is no definitive treatment available yet for the latter. In an effort to improve research, education, and medical and follow-up care, a number of registries have been set up for high-risk families (36).

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Ethical Differences Between Socialized and HMO Systems

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Abstract

A visiting scholar from the School of Philosophy of Leeds University, England, was invited to participate in a seminar at the Section of Bioethics of Drexel University School of Medicine, which discussed (a) ethical differences between socialized and HMO systems, (b) physician-assisted suicide, (c) reproductive technology, (d) triage and rationing, and (e) organ donation and sale.
Key Words: Medical ethics, HMO, socialized medicine, physician-assisted suicide, reproductive technology, triage, rationing, organ donation, ethics.

Differences Between HMO and Socialized Systems

DR. SAVITZ: PHYSICIANS ARE regularly involved in making decisions that affect the lives of their patients. In effect, doctors are called upon to apply ethical considerations with regard to the various illnesses encountered in their practice of medicine. The terms "ethics" and "morals" are often used interchangeably, but morality is a set of personal standards arising from family background, religious training and social rules, whereas ethics is a philosophical discipline concerned with what we ought to do, based upon reason and objectivity.

It bothers me a great deal to see how much technology is taking over medicine and how little dialogue is actually taking place regarding ethical considerations of particular cases. My son just finished his internship at a Harvard-affiliated hospital in Boston, and after 12-hour shifts the following ritual would take place. The incoming staff would meet the outgoing staff; no word would be exchanged; they would all hold up their palm-corders, which would electronically talk to each other and give reports; and that would be the end of any daily en-

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counter these groups might have. I worry about that kind of ritual, and I think that medicine is losing a great deal. If there is no time to transmit the information gleaned from patients and family, then there will certainly never be any time for ethical considerations among fellow physicians.

Much of this behavior has emerged because of our present health care system in the United States. In order to reduce the rapidly rising cost of medical treatment, sound business practices have been applied to the bills presented by hospitals, doctors and other health care professionals. The government had already set fees for service for Medicare, the elderly, Medicaid, the care of the indigent, Worker's Compensation, the care of injured workers, and no-fault (the care for those injured in a moving vehicular accident). Fees for service were now to be universally determined by insurance companies for the average American who required a medical checkup or actual medical or surgical treatment. Business practices that lowered premiums included contracting their physicians and hospitals to limit intake for care, reducing the fees submitted for care to 50–80% of previously prevailing rates, confining policy holders to health care professionals in the facilities within each plan, restraining efforts to discuss optional or better treatments from outside the plan, and using managers with no medical background whatsoever to make decisions.

Very quickly the problem with health maintenance organizations (HMO) became obvious. The patients could not choose their own family physicians or hospitals unless they had contracted with their plan. Referral to specialists and radiologic testing was under the control of doctors who were constrained by contracts that contained provisions to withhold payment if guidelines were not obeyed. Individuals in distress with colic, chest pain, and rotating back pain who came to the emergency room without notifying their HMO became responsible for the costs generated by the emergency care physician who ordered the required tests and did not obey cost constraints (unless the patients were admitted to an intensive care unit or underwent emergency surgery). Mothers were sent home 24 hours after uncomplicated vaginal delivery. Agism or discrimination by the age of the patient was tacitly in effect. The enormous profits generated by such sound business practices were not used to reduce premiums, but rather to fatten the paychecks of the managers and to increase the returns to shareholders of the HMOs.

In contrast, the Canadian health care system is often touted as a method of providing comprehensive medical care without private funding. Yet few Americans would tolerate its rationing of quality care or of kidney dialysis machines, its waiting lists for surgery, its lack of choice in assigned physicians. Even fewer know that when the annual governmental budget runs out of money, by November, most Canadian doctors go on vacations to warmer climates, and all elective health care ceases until January, when new governmental funds become available. In effect, dissatisfied Canadians, affluent Canadians, and sometimes Canadians with emergent conditions will actually cross the border and come to the United States. These facts, of course, are not mentioned by anyone who favors the Canadian system. But neither the American system nor the Canadian system is anything like the National Health Service in England. Dr. Rivlin, who is with us today, lives in the United Kingdom, has actually been treated by the National Health Service, and will give us an overview of the National Health System in England.

Dr. Rivlin: Recently, there has been a seismic change in medicine in the U.K.—it has nothing to do with any new drug or treatment, but rather with the shift from paternalism and "doctor knows best" to the power of the patient. Or to simplify, patient autonomy has taken its place. The increasing availability of information via the Internet coupled with a tendency toward greater individual rights means that patients will inevitably want to have a far greater input into the way they are treated, in both the medical and ethical sense. Respect for autonomy requires that patients be given sufficient information to make an informed choice about treatment. Failure to get informed consent from a patient would leave a doctor open to charges of assault and battery.

In English law, there are three things that must be in place for legally valid informed consent or refusal of medical treatment: the patient must be competent to consent or refuse, the consent or refusal must be based upon adequate information, and the consent or refusal must be given voluntarily. And there is a major difference between United States and English law [with respect to how much information is adequate]. In the U.S., the test is what would a reasonable patient expect in a given situation, whereas in England the test is what a reasonable doctor would provide in a given situation. The seminal case in English law is that of Bolam, decided in 1957 (1). The lawsuit concerned a patient receiving electroconvulsive treatment which caused his limbs to flex violently. The defendant doctor took no precautionary measures, and his patient suffered serious damage to his thighs and hips when the treatment propelled him from his hospital bed onto the floor. In his summation, the judge instructed the jury that "a doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art" (2). One of the problems for doctors is to know how much information they should give regarding risk of a procedure, for consent to be deemed informed. If a doctor tells a patient of all possible risks, however remote, the patient might worry to such an extent that recovery is hindered. In a famous case, a Mrs. Sidaway complained to the courts that she would not have had an operation had she known of the remote risk of severe disablement (3). The judge, relying on the Bolam case, said that a doctor's obligation was only to give her information that a responsible member of the medical profession would think it proper to give.

Only recently has the National Health Service admitted that rationing is needed. In England, health care funds are allocated on a "macro" basis (governmental or regional) and a "micro" basis (controlled by general practitioners). In the past, the government allocated a budget in trust and allowed health authorities to allocate the funds within the localities for which they were responsible, and that is still the case for most of the funds. Recently, however, the government set up the National Institute for Clinical Excellence (NICE) to take a more active role in the decision-making process for individual drugs and treatments. The idea was to make cost effective procedures available nationally. However, the government does not always make extra funds available to pay for what the NICE recommends. The trust and health authorities in the hospitals have respectfully declined to live within their budgets, but they are not allowed to overspend. The result is that the government has a reserve lifeboat on a sinking ship providing passengers with additional means of being saved. In other words, if the NICE says that interferon should be given to every patient with multiple sclerosis, the government does not provide extra money, so the money for interferon has to come from somewhere else in the National Health Service (NHS). Another way in which health care funds are distributed is by general practitioners. The NHS employs them, but as independent contractors. A doctor has an obligation to provide primary medical care to his or her patients. However, general practitioners will argue that they simply cannot adequately treat or care for all their patients, because there are not enough funds available. Of course, patients will be seen by their doctors, but there is no guarantee that they will receive the best treatment that is available or that they will not have to wait a significant length of time to be treated. It should also be noted here that doctors can remove any patient from his or her list without giving reasons to the patient for doing so.

In France, there is no such thing as waiting for treatment—they have twice the number of doctors and hospital beds per capita. The main reason for this disparity is that the French are prepared to pay much higher taxes and more money out of their own pockets. The truism that you get what you pay for applies to health care. Why are we so unwilling in the U.K. to spend more on such an important service? First, in my opinion, we are essentially a selfish nation and do not like the idea of paying more taxes, even if it will benefit us ultimately. Whenever a political party has gone into an election saying they would increase taxes for the benefit of health and education, that party has lost. Politics is based on a short-term outlet. Politicians want to get elected. Second, for years the public was told both by the government and the medical profession that the U.K. has the best health service in the world. The public believed this report and, as a result, saw no reason to pay more taxes to increase funding for the NHS. Third, about 6.2 million (about 8% of the population) buy private medical insurance and are able to "jump the queue." These people, often from the higher socioeconomic group, are the very ones who complain about the NHS if they have no alternative.

What can be done to improve the National Health Service? Substantially more money will have to be spent. These funds could come either from increased taxation or by moving funds from other areas of government. More patients might travel to France and Germany for treatment, where there is an oversupply of facilities, especially in view of the recent ruling from the European Court of Justice (4). The NHS does provide a limited safety net for the general population. Most people who need treatment for life-threatening conditions will eventually get it—though not always the treatment they need or when they need it. I am informed that there are more than 40 million people in the United States who do not have health insurance. In England, they would certainly get treatment eventually. All patients would get to see a general practitioner even if they had to wait a few days for an appointment, or be attended to in an emergency department after waiting 8–9 hours to be treated. Improving the socioeconomic status of poor people may come down to a choice between more health care facilities and improving the education, diet, and health habits, such as smoking and drinking, of the general population.

The care of the infirm and elderly in the U.K. is sorely lacking in governmental funding, but is shored up a great deal by private charitable donations for hospices and nursing homes. The government has decreed that agism should be banished from the NHS. It should be obvious that elderly people are not a group of identical people, but are individuals, some of whom will gain greatly from treatment and some of whom will not. Agist policies suggests that one section of society can be dispensed with, something that runs counter to centuries of medical teaching and has profound and disturbing implications both for the doctor-patient relationship and for the practice of medicine as a whole.

Physician-Assisted Suicide

Dr Savitz: The U.S. Supreme Court left it up to each state to pass legislation allowing physician-assisted suicide by saying that in such cases the patient's rights outweigh the state's interest. Some states have proposed acts to legalize physician-assisted suicide, but so far only Oregon has passed such a law. The requirements are very rigid, as you might imagine, and appropriately so. The patient has to be 18 years of age or older and have legal capacity. No one who is unconscious or retarded, or who cannot otherwise express his or her own wishes may make such a request. The person must be a resident of Oregon. The diagnosis must be a terminal, incurable, and irreversible illness that will lead to death within 6 months. The consulting physician has to concur with that diagnosis, and two additional physicians must agree to the option. The patient has to be advised of palliative care options, especially pain control. One cannot just move to Oregon on a Thursday and get physician-assisted suicide on Friday.

Dr. Fleetwood: Jack Kevorkian, a pathologist, is probably the best-known physician who has been a strong supporter and vocal advocate of what he calls physician-assisted suicide. But actually, the kind of thing that Kevorkian is doing and the reason he is in prison today is not physician-assisted suicide at all. His initial attempts were at what he termed euthanasia—providing for a quick death for people who did qualify for physician-assisted suicide under the definitions that most people knew. The American Medical Association (AMA) definition of physician-assisted suicide is a doctor facilitating a patient's death by providing the necessary means and/or information to enable the patient to perform a life-ending act. That means was a prescription or even in some cases information on how a patient might kill himself or herself. The patient performed the life-ending act by swallowing the pill or pushing the button that started the lethal intravenous injection. Initially, Kevorkian followed these guidelines. He is in prison because he went one step beyond that and actually pushed a button to start a drug that killed the patient. It is important to think about this distinction, because we are talking about suicide and not murder by your newly found friendly physician.

The term "life-sustaining treatment" is often confused in the literature. Any therapy that serves to prolong life without reversing the underlying medical condition—a ventilator, nutrition or hydration provided by tubes, or any number of things—could qualify as life-sustaining treatment. Withdrawing life-sustaining treatment is considered legally and ethically permissible in the U.S. as long as the patient has decision-making capacity. In fact, the law says that physicians have to respect competent patients' wishes to refuse life-sustaining treatment.

Our case study focuses on three patients. A patient in the U.S. with terminal lung cancer and bone metastases has exhausted all treatment options and suffers from intractable pain despite hospice treatment. He has decisional capacity and has requested a prescription from his physician to use in committing suicide. Another patient, a resident of England, also has lung cancer with bone metastases. He also has exhausted all treatment options and suffers intractable pain despite hospice treatment. He has decisional capacity and has requested a prescription from his doctors to commit suicide. The third patient, living in Oregon, suffers from terminal lung cancer and bone metastases, has exhausted all treatment options, and suffers from intractable pain despite hospice treatment. She has decisional capacity and has requested a prescription from her physician, for assisted suicide. According to anonymous independent studies, the U.S. patient, where physician-assisted suicide is against the law, may find a physician willing to prescribe drugs in nonlethal doses while knowing that the patient intends to commit suicide by taking an overdose. The patient in England will have a hard time going to a physician, making clear what his intentions are and getting the physician to write the prescription. As for the third patient, she qualifies to go to a physician who is willing, and receive a prescription that she can then use for physician-assisted suicide.

There is a history here that is largely overlooked, changes in how people approach euthanasia and physician-assisted suicide. When you look back at ancient Greece and Rome, you see that euthanasia was really widely accepted initially. Physicians gave their patients poison when they were suffering and dying. They thought that relieving suffering was an important part of their job. However, some physicians became part of the Hippocratic School and swore never to give anyone a drug that would cause death. The Christian view was that one's life was held in trust from God, that one's body was a vessel inhabited for a period of time, that killing oneself was immoral and assisted suicide even more immoral. From the 12th through the 15th centuries, there was consistent opposition to euthanasia among physicians throughout Europe. With the advent of anesthesia in the 1800s, people really started thinking about using ether to mitigate the agony of death and not just the pain of surgery. By the 1870s, Samuel Williams suggested the use of chloroform and other drugs to hasten death. In 1885, in the *Journal of the American Medical Association*, Williams' proposal was characterized as an attempt to "make the physician down the road be an executioner." Suddenly you can see that there was a debate whether ether and other drugs should be used to ease people's passage before death.

One argument against physician-assisted suicide is that it would be difficult to limit—sort of a slippery slope. If you accept physician-assisted suicide by patients who voluntarily agree and are willing and able to take the lethal drug themselves, what happens with patients who are not so able, are retarded or have limited ability to understand what is going on? Once you accept physician-assisted suicide, you will inevitably slide down the slippery slope of accepting other patients.

Another argument, one which is actually more persuasive, is that palliative care may receive less consideration if physician-assisted suicide is a legal alternative. The funding for palliative care and teaching it in medical school will get shorter shrift than it already does. Yet another argument is that legalization would undermine the patient-physician relationship and the trust necessary to sustain it, throughout the medical profession and society, and endanger the value our society places on life, especially on the lives of the disabled, incompetent, and terminally ill.

Dr. Rivlin: In the United Kingdom, euthanasia and physician-assisted suicide are illegal. Doctors who have given patients a lethal dose with the intention of ending the patient's life have been charged with murder, although suicide is not illegal. Also, just like in the U.S., the option of withdrawing life support is acceptable. Life-sustaining treatment can be withdrawn from a patient who does not want to be on a ventilator, without committing physician-assisted suicide.

The British Medical Association supports the distinction between relieving suffering and literally killing somebody.

A flurry of articles recently looked at terminal sedation, that is, sedating a terminally ill patient to unconsciousness and withdrawing nutrition and hydration, so that he or she eventually dies without ever waking up from the sedation. Removal of nutrition and hydration which are not beneficial to the patient is permitted. Is terminal sedation physician-assisted suicide? The patient is not performing a life-ending act. Should terminal sedation become a viable option when pain is truly serious and intractable?

Anthony Bland was a young man of 18 who was crushed in a soccer match. He ended up in a persistent vegetative state. His parents and doctors went to court and asked for permission to withdraw the feeding tube, with the certain knowledge that this act would cause his death. It went through all three British court systems and ended up in the House of Lords, which is equivalent to the U.S. Supreme Court. The House of Lords decided to permit the cessation of his artificial feeding; however, the Lords emphasized that it would be illegal to kill Bland by lethal injection or by commission. Artificial feeding is medical treatment. Medical treatment should be given only if it is in the patient's best interest. Once there is no hope of recovery, it cannot be in the best interest of the patient to receive treatment. There is no obligation for the doctor to give treatment that is futile. Nevertheless, there was another major hurdle for the doctors to overcome. As noted, killing by commission is illegal. Could it not be argued that withdrawing the nasogastric tube was an act and therefore illegal? The five judges approached this matter in various ways. In general, they decided that it was impossible to distinguish between not starting nasogastric feeding, which would of course be an omission, or withdrawing the feeding tube once it was in place.

The issue of euthanasia is coming to the courts soon in England. The case concerns Mrs. Diane Pretty, who suffers from end-stage renal disease and wants to die at home at the time of her choosing, with her husband's help. She has gone to court to challenge the refusal of the Director of Public Prosecutions to rule out prosecution of her husband if he assists her in killing herself. Mrs. Pretty argues that the government has subjected her to degrading treatment in forcing her to live. The judge has allowed this case to go forward to judicial review. If Mrs. Pretty succeeds in her claim, then the courts will be sanctioning euthanasia by commission. I would be very surprised if the courts granted her wish. What they are likely to do is leave it for Parliament to decide, if Parliament wants to change the law. This case is going to be the most important one concerning euthanasia that we have seen in England in the last decade[1]. One last comment from me, as someone who thinks the slippery slope argument is very persuasive—few cases (29 cases in each of the last 3 years) have succeeded in obtaining permission for physician-assisted suicide in Oregon.

Reproductive Technology

Dr. Savitz: It is very interesting for me to have lived through all of the changes in genetic technology that have taken place. We have all become used to the fact that it is possible to have test tube babies, Petrie dish conception, and surrogates (women who carry the fetus to term but neither are the biological mother nor have an interest in adopting the child). The most fascinating case is that of the Buzonga family, a relatively wealthy couple. After a suitable work-up and a number of tries, it was found that neither the husband nor the wife could be a biological parent. (He had problems with low sperm count and she with endometriosis.) In effect, they purchased sperm and found an egg donor. They further went to the trouble of finding a surrogate, named Pamela. All went well. The fetus was conceived and implanted, and the gestation was going on when the couple divorced. At that point, they decided that neither one of them wanted the child after it was born. The courts ruled, for the first time in history, that this child truly had no legal parent. How it all resolved isn't surprising, namely, a fund was finally set up by the wealthy parents to support the child even though neither one of them wanted to adopt him. Tinkering with Mother Nature can result in problems, and you are going to hear further on this subject from Dr. Connie Perry.

Dr. Perry: The case of the Buzongas and other cases of reproductive technology are really my areas of expertise and primary interest. However, since we are comparing the United Kingdom and the United States, I thought I would focus on cloning and stem cell technology, because of the major differences of opinion. In January of this year, the British Parliament passed legislation to extend authorization of research on human embryos. Previously, human embryo research in the U.K. was limited to research questions involving reproduction, fertility, and embryology. This act includes allowing the use of cloning technology to create embryos for research purposes and to enable any such knowledge to be applied to developing treatment for serious disease. In all such cases, researchers proposing to use embryos must prove to the Human Fertilization and Embryologists Authority (HFEA) that the use of embryos is necessary for research purposes. Unlike the U.S., there are extensive protections for the patients in the U.K. For example, there are statutory limits on the storage of embryos. A number of steps are taken to ensure voluntary consent and even posthumous use. Prior to submission to the HFEA, proposals need to be approved by multiple centers or a local research ethics committee, not unlike our Institutional Review Board.

The difference between United Kingdom committees and ours is that the U.K. committee is required to be more independent from research institutions. No more than one-third of the committee members can be from or have a financial interest in the institution in question. Furthermore, the chair of the committee must be entirely independent. In the U.S., peer review occurs only for proposals that require grants for funding, and the fertility industry is largely unregulated. On July 31, 2001, the U.S. House of Representatives passed the Human Cloning Prohibition Act, prohibiting the creation and use of human clones for any purpose. President Bush announced his decision to allow federal funding for limited embryo stem cell research with existing embryonic stem cell lines.

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[1] Since the seminar was held, the House of Lords ruled that Mrs. Pretty's husband could not be granted immunity from prosecution if he helped his wife to die [2001 2 WLR 1598]. Mrs. Pretty subsequently appealed to the European Court of Human Rights but that court endorsed the House of Lords' decision [Pretty v. The United Kingdom, No. 2346/02, European Court of Human Rights, 4/29/02.]

In my opinion, the resistance to the use of cloning to create embryos for research is based largely on a "gut level" reaction rather than on careful analysis. Cloning creates the fear of engineering of humans and of playing God. The "playing God" concern invokes the question of naturalness and argues against most medical practices. A person in respiratory arrest will naturally follow the course toward cardiac arrest unless there is a divine or human intervention. To avoid playing God, one could argue that one should leave these situations to the divine. In the U.S., belief in the freedom of religion implies that to impose a law based solely on one's religious interpretation would violate the rights of others and those with other beliefs. But is the argument against creating embryos through cloning based only on that religious stand against unnaturalness? There is also the fear of engineering humans or creating cloned people; therefore, the law is meant to prevent any cloned embryos from becoming sentient beings. The risk of pain and suffering is not an issue. The true problem is advancement of technology that would allow the creation of a whole person merely for the use of others. However, this argument can be used against many technologies. Research on medications can create knowledge that can harm as well as help individuals. In learning how to save a life, one also learns how to end a life. The difficulty with the argument that benefits of embryonic stem cell research outweigh the risk is the fact that the real benefits are unknown and unknowable without actually using the technology of human research. There are a number of conditions for which stem cell research shows great promise. The point of this talk is that we need to examine whether embryos have moral status before they become sentient beings. If such embryos cannot be used as a mere means to an end, then we cannot destroy them even for the innocent purpose of curing serious disease and injury. To restrict an individual's or a couple's voluntary choice to donate leftover embryos for research, the government wants to impose a specific moral principle. Given that these embryos are not going to develop into members of the public, the public should have no say in their disposal since it is perfectly legal and even desirable for these couples to destroy the embryos that are no longer candidates for gestation nor desired for implantation, nor being donated to other infertile individuals.

Triage and Rationing

Dr. Savitz: The idea for triage should be accredited to Napoleon's chief surgeon, Baron Dominique Jean Marie. A system of ambulances transported injured soldiers to field hospitals on the basis of wound severity rather than military rank, which had previously been the sole basis for transporting the wounded. Soldiers who were in need of and could be saved by surgery were now given priority. Next, military personal requiring first aid were treated. Lastly, those expected to die of their wounds were made comfortable, if possible. If anyone thinks that this doesn't have meaning, September 11 made it very clear that triage is still an essential element of health care. The concept of triage also comes into play when you have a single patient who presents with brain, chest, abdominal, and/or orthopedic injuries and thus requires more than one specialist. If those specialists are treating one patient, then obviously they cannot be distributed among many patients who require specialized, but individualized treatment. It is interesting to note that in the dictionary the verb "ration" has two definitions. One "is to use sparingly" and the other is "to distribute equitably." Those of you who have studied rationing know that you have to get both definitions to work.

A final note: It has been my privilege to have lectured in a number of countries and I especially remember a visit to the Kantonspital Zurich, the main hospital in Zurich, Switzerland. There was a veranda, and every day, whether it snowed or it was sunny, every patient was bundled up in blankets and brought outside. The veranda overlooked a park. The Swiss specifically built parks around their hospitals, where children would play, and as long as patients were alive they were exposed to life.

Dr. Rivlin: Rationing in England takes place in a number of ways. The first way is by waiting lists. In England, there can be long waits for treatment of even serious conditions. If the general practitioner sends the patient for a hip replacement, it could take three years for a patient to be scheduled. In addition, the patient might have to wait 12 months to get an appointment with a consultant. Overall, it could take 3–4 years to get a hip replacement. Patients have to wait not only for non-life-threatening conditions; many patients with chronic obstructive pulmonary disease do not get to see a consultant quickly enough and die as a result. The second method of rationing is by the doctor not informing patients that there are drugs and treatments that would help them. The third method is by cost saving that occurs when the patients do not receive the necessary drugs or treatment because they are too costly. It was reported in the *Financial Times* only last month that the National Institute For Clinical Excellence has decided to reject the widespread use of interferon because it is too expensive (5). Even though the clinical effectiveness is proven, the cost effectiveness is not. According to the Multiple Sclerosis Society, only 2–3% of multiple sclerosis sufferers in England receive treatment with interferon, compared to 12–15% in many other European countries (6). Another way of saving money is by not replacing out-of-date equipment. Many of the X-ray machines in England are very old, and there is such a shortage of MRI scanners that getting an appointment, even as a private patient, can take 3 weeks or longer.

I want to refer briefly to something that could put the government in a very difficult situation regarding the rationing of health care, namely the new Human Rights Act from the European Parliament. Article 11 of the Human Rights Act provides for everyone's right to life to be protected by law. This absolute right makes no exception on grounds of lack of funds. When a patient has been refused a drug for reasons of cost, steps may be taken to challenge the decision as incompatible with Article 11, since withholding the drug treatment could lead to an earlier death. No patient has yet made such a challenge.

Organ Donation and Sales

Dr. Savitz: There is a new market which is growing fast in today's global economy—the market in human organs to be used for transplants. For the last 30 years, organ transplants have become more and more commonplace. As the demand for organs increases, so does the need to find more donors. All of us are aware that some cadaveric organs can be used. You should also be aware that the American Medical Association is presently backing a plan by which people could donate their organs upon their death, but money would be paid to their family or anyone else that they designate. In the meantime, it has come to the press's attention that in China the organs of condemned prisoners are removed before they are executed and the organs are then sold on the open market. In India, poor people sell their organs in order to purchase items they could never afford otherwise, from tractors to dowries for their daughters. In Brazil, it is not uncommon for the wealthy to buy organs from members of Indian tribes and then claim they had received them from poor relatives.

Dr. Caputo: In China, even political prisoners may be executed; and they are shot in the head to prevent the loss of any organs. Surgical harvesting may unceremoniously take place in the field—an act that is quite horrible. I think this subject has given us a perfect sequel to talking about rationing, because in the U.S. we are convinced that if we throw enough resources at a problem, we can fix it. When there is something wrong with an organization, no matter how much money we are pouring into it, somehow more money is found to fix it.

You can buy a liver, but there are just so many livers in the marketplace. What is the problem with organ sales? The problem is that there are a lot of people waiting, and increasingly more people waiting over time. Why? We are getting better at transplantation. We have anti-rejection drugs that are getting more and more effective. We are able to get organs into people who are older and less medically stable. The other side of the coin is how many organs are being put on the table, so to speak—not enough to meet the demand. What strategies are being planned? From one person, you may get a liver, a heart, two kidneys, and a pancreas; but supply and demand studies indicate that some patients are dying while waiting. The number of cadaver and living donors continues to go up and up, but the resources remain limited.

Philosophers may ask, "How can we treat this situation?" The prevailing concept is something called distributive justice. How can we be fair? We talk about rationing, we talk about allocation, and we have numerous would-be recipients. You say, "Let's do the most good or cause the least harm that we can for the greatest number of people, all at once. Let's treat everybody truly equally with our blinders on." If you were to talk about totalitarianism, you might say that the only fairness is saving no one; but if you give priority to saving everybody, then maybe you should employ the principle of medical neediness. Should you give priority to those who are medically needy, to those who are most helpless, or to those who are first-come? Egalitarianism, utilitarianism, totalitarianism—are philosophers going to come up with the answer?

What about organ sales or other financial incentives? In Great Britain, organ sales are absolutely illegal. In the United States, it is not allowed, but people are starting to think about its legalization. In Pennsylvania for example, there was a proposal to pay $300.00 to the family of the organ donors for funeral expenses. A lot of civil libertarians argue that "it's my body and if I want to give up one of my kidneys, it's my right." On the other hand, what will happen if we start making an organ market legal? People may ask why they should give up a kidney freely if they can get $5,000 – 15,000 for it. In other countries, such as Belgium and Switzerland, there is a presumed consent mechanism: it is understood that organs will be donated unless the deceased has left instructions to the contrary.

How are most decisions about transplantation made in the United States? In general, most of the decisions are based on a specific patient who is about to die, the likelihood of success, how good the match is, the relative sizes of donor and recipient, and geographic proximity. First, the physician puts the patient on a national registry list. If the surgeon who makes his or her own medical assessment decides that the patient will never adjust to the anti-rejection drugs, he or she won't put the patient on the list. Other factors include addiction. A smoker who cannot stop smoking before the heart transplant will not be placed very high on the list.

Dr. Rivlin: A couple of interesting cases have come out of England recently regarding transplantation. In Sheffield, a white patient donated his kidney on the condition that it should only be given to another white person. His bequest was accepted, but there was an outcry in the press, and the government said that under no circumstances could that ever happen again. The general practitioner said that he would accept the donation so that he wouldn't have to tell the mother that her 15-year-old son could not get a kidney because of some vague philosophical principle. The second matter concerns a group of people who are willing to accept organs, but not give them. Some Orthodox Jewish people maintain that they have to be buried whole, but an organ donation is acceptable to save the life of one of its members. The question to think about is that if somebody is not willing to donate organs, should they be allowed to be eligible to receive organs? I am not offering answers, just making an ethical point.

Dr. Savitz: I want to thank you all for attending our seminar, and I hope you won't mind if I finish with one of my favorite modern parables, which concerns the young mouse who came upon an old lion crying in the jungle. "What's wrong?" said the mouse. "I can't walk," replied the lion, "because I have a thorn in my paw. Could you pull it out for me?" "Nonsense," said the mouse, "Stop acting like a baby. Everybody has a little pain, it builds character. I am sure that the thorn will fall out by itself eventually. In the meantime, stop walking around on it. The hurt will stop after a while and you will be just fine." So the old lion limped off into the jungle and the young mouse started his own HMO.

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Carpal Tunnel Release:

Using a Short Vertical Incision above the Flexor Crease of the Wrist

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Abstract

Background: Numerous surgical incision techniques have been used to treat carpal tunnel syndrome. The advantages and disadvantages of each are a matter of debate. However, the technique should be cost effective and also decrease the amount of time needed before the patient can return to work. A minimally invasive surgical procedure for the treatment of carpal tunnel syndrome is described in this report.
Methods: Ninety-six patients with carpal tunnel syndrome (106 wrists) were operated on through a 2 cm vertical incision, above the flexor crease of the wrist, under local infiltration anesthesia, without tourniquet control. The mean time length of the operation was nine minutes.
Results: Numbness and night pain disappeared in all cases postoperatively. The mean time period to return to work and full activity was 18 (12 – 26) days.
Conclusion: Decreasing the time needed before the patient can return to work, minimizing the rate of complications and reducing hospital costs are advantages of this technique.
Key Words: Carpal tunnel syndrome, carpal tunnel release, median nerve entrapment.

Introduction

NUMEROUS SURGICAL INCISION TECHNIQUES have been used to treat carpal tunnel syndrome (CTS), such as the classical open releasing technique, a short palmar incision and the endoscopic method. The advantages and disadvantages of each are a matter of debate (1 – 6), but their common goal is to release the median nerve by transectioning the transverse carpal ligament (TCL). And whatever the technique, the palmar cutaneous and recurrent motor branches of the median nerve and the superficial palmar arch must be protected during the operation. Also, the technique should be cost effective and decrease the amount of time needed before the patient can return to work. Healing uneventfully and avoiding late complications like scar tenderness and pillar pain should likewise be kept in mind.

In this report, we describe a minimally invasive procedure through a 2 cm vertical incision, above the flexor crease of the wrist. This approach allows surgeons to perform outpatient surgery using local infiltration anesthesia (LIA), thereby eliminating the need for a tourniquet. Hospitalization is also not needed.

Materials and Methods

Ninety-six patients underwent carpal tunnel decompression (106 wrists) using this technique, between January 1998 and May 2003. Fifty-eight patients were female and 38 were male. The mean age was 44 years (24 – 72). Surgery was performed on the right hand in 49 patients, on the left in 27 and bilaterally in 20. The mean follow-up period was 24 (12 – 50) months. We based the diagnosis on patient's history and subjective complaints of numbness and increasing pain at night. Phalen's maneuver, Tinel's sign and grip strength were also noted. The diagnosis was confirmed by electromyographic study (EMG) preoperatively. Splinting, physical therapy and non-steroidal anti-inflammatory drugs (NSAIDs) were used as the first choice of treatment for all cases. Surgical treatment was planned for patients

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with persistent CTS. The Boston self-administered questionnaire was used for the assessment of severity of symptoms and functional status for both preoperative and postoperative evaluations (7). Outcome measures were analyzed with the SPSS program.

This technique was initially practiced on cadavers. A 2 cm vertical incision above the flexor crease, corresponding to the proximal part of the classical incision, was done on twelve wrists in six cadavers. Transection of the TCL was performed through this approach percutaneously. After that, the incision was extended distally and the procedure was converted to the classical open technique. The adjacent tissues were examined and the effectiveness of the release was checked directly. No injuries of the recurrent motor and palmar cutaneous branches of the median nerve and the superficial palmar arch were noted. In three wrists, the transection of the TCL was found to be incomplete distally. Checking the TCL with a blunt hook has been used as an essential step of the procedure since then.

Surgical Technique

The operation is carried out under LIA. The 2 cm incision is on the ulnar side of the palmaris longus, above the flexor crease of the wrist, and should be extended 5 mm distal to the flexor crease. Thus, the median nerve and TCL are visualized. Following the incision (Figure), the palmaris longus tendon is retracted radially to protect the palmar cutaneous branch of the median nerve. A clamp is placed between the ligament and the nerve for protection and the TCL is transected with a no. 15 blade, with the sharp side up, beginning through the incision from proximal to distal, percutaneously. The resistance of the TCL can easily be felt during the transection. Particular attention should be paid when approaching the distal end of the ligament. After completion, the blade is removed and the TCL is checked with a blunt hook before it is released. Tissues are closed properly.

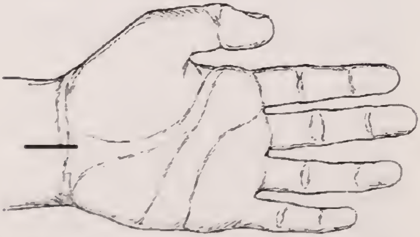

Figure. Short vertical incision above the flexor crease of the wrist

The mean operating time was 9 minutes. Bleeding problems were not observed. A compression bandage was used postoperatively, without the use of a splint. A waterproof covering was applied on the first postoperative day. Active motion of the wrist was encouraged.

Results

All patients were seen 1, 3, 6 and 12 months postoperatively. A physical examination was done. Patients' satisfaction and adjustment to daily activities were recorded, based on the Boston Questionnaire. Scores of symptom severity and functional status were obtained both pre- and postoperatively, and were analyzed. The mean symptom severity score improved from 3.8 (±0.4) to 1.6 (±0.3) and the mean Functional Status score improved from 3.9 (±0.3) to 2.0 (±0.3) on the third month postoperatively. Significant recovery of the patients was noted both functionally ($p<0.001$) and symptomatically ($p<0.001$) (Wilcoxon signed ranks test).

Hypertrophic scar formation was noted in six cases. This resolved with massage and silicone sheet application, in three months. One patient had pillar pain, which resolved by the sixth postoperative month. Numbness and night pain resolved in all cases. The mean period to return to work and full activity was 18 (12–26) days. Eighty-five percent of the cases had full grip strength back by the third month postoperatively. Improvements of sensory and motor nerve conducting velocity were noted at the twelfth month postoperatively.

Discussion

The surgical treatment techniques of CTS can be classified as either open or endoscopic. The goals of both techniques are to transect the TCL completely without damaging the adjacent structures and to allow the patient to return to work as soon as possible. During the operation, the palmar cutaneous branch; the recurrent branches of the median nerve, ulnar nerve, ulnar artery, superficial palmar arch; and the communicating branches of the ulnar nerve are potentially at risk (2, 5, 8). Complications associated with injury to these structures are reported at rates of 5–15% for the open technique and 2–35% for endoscopic surgery (9–11). The open technique is relatively inexpensive, and vulnerable structures can be easily visualized throughout the procedure, but disadvantages include scar tenderness, pillar pain and a longer period before return to work (2, 4). Endoscopic technique offers the advantage of a shorter period before return to work; however, it has the disadvantages of being an expensive procedure with increased risk of damage to the adjacent tissues and incomplete transection of the TCL (1, 5, 6, 12).

Serra et al. described an open technique that decreased the time to return to work and minimized morbidity (4). The cases were treated through a short palmar incision, and no hypertrophic scar was observed. All patients resumed their daily activities the first week postoperatively. In that study, 104 of 112 patients returned to work within 3 weeks after the operation. Serra claimed that the technique had all the advantages of both open and endoscopic techniques. Mackenzie et al. performed the same technique and compared it with the endoscopic method. He reported that endoscopic carpal tunnel release (CTR) using the single portal provided better results as compared to short-incision, open CTR (13). Our results are similar to those of open CTR with short incision and endoscopic CTR using the single portal.

The short length of the incision decreases the time to return to work. Every 1 cm increase in the length of the incision prolongs the time to return to work by nearly 5 days (14). Our incision is fairly short and, moreover, it is not in the palmar area. No complaints associated with daily activities were observed. Although no predilection for hypertrophic scar formation was reported for this region, this complication did appear in 5.5% of the cases; all were solved by simple treatment methods. This technique provides faster recovery of grip strength, and it protects the palmar fascia and the skin above the interthenar crease, so that the neuroma formation leading to scar tenderness is prevented.

The diagnosis of CTS was based on history, complaints of the patient and physical findings, indicated as positive Phalen's maneuver and Tinel's sign. Measurements of the hand grip and pinch strength were not useful tests for differential diagnosis. These tests consistently had the lowest specificity and sensitivity, and predictive values (15, 16). Some authors support a combination of clinical history and physical examination as the primary method of diagnosing CTS, claiming that EMG confirmation is unnecessary in most cases (16). However, we routinely perform EMG as an objective diagnosing test, in order to evaluate both the median nerve and the ulnar nerve, as well as the recurrence of the CTS. In Trumble's opinion, surgery is unnecessary for the EMG-negative cases (12). All cases that were treated surgically had positive EMG results, supporting CTS.

A vertical incision above the flexor crease of the wrist allows better visualization than does the transverse incision. The transverse incision also has a higher risk of damaging the cutaneous palmar branch of the median nerve, and in addition, most of the anatomical variations and congenital anomalies of the nerve cannot be seen through it (17, 18).

Mesgarzadeh et al. noted four general findings by MRI in CTS, regardless of the etiology: swelling of the median nerve, flattening of the nerve at the hamate level, palmar bowing of the flexor retinaculum, and increased T2 signal of median nerve. Two of these changes, swelling and flattening of the nerve, can be seen directly through our approach (19).

Conclusion

This prospective study was planned because of the need for developing a practical exposure for release of carpal tunnel compression syndrome. With this technique, clinical recovery is rapid and the quality of life of the patients is quite good during the healing period. Outpatient surgery, use of LIA, and avoidance of a tourniquet are additional advantages of the technique. Moreover, no specialized equipment is needed for this procedure, and costs are relatively low.

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Ultrastructural Changes in Rat Liver Treated with Pralidoxime Following Acute Organophosphate Poisoning

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Abstract

We investigated the ultrastructural effects of methamidophos and the positive effects of 2-pralidoxime (2-PAM) on the liver. Male Wistar-albino rats were assigned to 4 groups and all were treated per os: Group 1 (n=10) received 30 mg/kg methamidophos; Group 2 (n=7) (serving as controls for Group 1) received physiologic NaCl; Group 3 (n=10) received 30 mg/kg methamidophos and was treated with 2-PAM and atropine when cholinergic symptoms were noted; and Group 4 (n=7) (serving as controls for Group 3) was treated with physiologic NaCl. Plasma cholinesterase was measured using radioimmunoassay. Liver tissues were prepared for electron microscopic studies. Methamidophos treatment of Group 1 led to serious changes in hepatocytes and organelles. These changes were not detected in Group 3. In Group 1, the chromatin content of some hepatocyte nuclei and cytoplasmic density increased; these cells also became vacuolar in appearance as a result of lysis in the mitochondrial matrices. In some cells, the lipid content constituted the majority of the cytoplasm. Furthermore, these cells were surrounded by glycogen accumulation. In some areas of the perisinusoidal zone, collagen fibers had increased to form bands. None of these changes were noted in Group 3. These findings suggest that acute organophosphate poisoning causes serious histopathological effects in rat liver, but that these changes are reversible with appropriate treatment strategies.

Key Words: Liver, organophosphate, pralidoxime, poisoning, treatment, ultrastructure, hepatotoxicity.

ORGANOPHOSPHATE INSECTICIDES are widely used in both agricultural and landscape pest control, and the potential for human exposure to this class of compounds is significant. The primary toxicity associated with acute exposure to organophosphate insecticides is cholinergic crisis resulting from acetylcholinesterase inhibition (1). However, these compounds also have numerous other specific effects, including delayed polyneuropathy, immunotoxicity and carcinogenesis, as well as endocrine, developmental and reproductive toxicity (2, 3). In the past, research efforts generally focused on neurobiological effects of these chemicals. A review of the literature indicates that peripheral organs such as the liver have been much less intensively studied. Yet it is well documented that numerous drugs and hepatotoxins elicit marked alterations in hepatocyte functioning (4).

The present study was undertaken to investigate whether administration of a single lethal dosage of methamidophos, a highly toxic organophosphate, induces any ultrastructural changes in murine hepatocytes, and to highlight the characteristics of the changes observed after treatment.

Materials And Methods

Thirty-four male Wistar albino rats, obtained from Çukurova University Medical Sciences Experimental Research Center, were used for the study. The rats weighed between 220 and 230 grams. They were housed five to a cage, with a room temperature of 22 ± 2°C and a light:dark cycle of 12 hours on and 12 hours off. Food and water were available ad libitum. Methamidophos [0,5-dimethyl phosphoramidothioate, median lethal dose (LD_{50}) = 30 mg/kg] with a purity of 99.1% was diluted in tap water to 30 mg/kg/mL and administered via gavage using a 20-gauge feeding needle. At-

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ropine sulfate and pralidoxime (2-PAM) were dissolved in saline and injected intraperitoneally (IP) with a 23-gauge needle. The animals were anesthetized with 75 mg/kg ketamine and 5 mg/kg xylazine intramuscularly (IM). The rats were sacrificed by intracardiac blood collecting. Each rat was treated and examined separately and independently. Blood samples were centrifuged in 1000 cycles for 10 minutes, and their plasmas were kept at – 70°C. Then the enzyme, pseudocholinesterase (PCE) underwent the same treatment. Assay was made by radioimmunoassay. The liver tissues were fixed in 5% glutaraldehyde in Millonig phosphate buffer at pH 7.4 for four hours and postfixed in 1% osmium tetroxide in phosphate buffer at pH 7.4 for 2 hours at 4°C. Tissues were dehydrated in graded ethanol and embedded in araldite. Thin sections were cut using Reichert Ultracut S ultramicrotome, stained with uranyl acetate and lead citrate, and then examined with a Zeiss EM 10B electron microscope.

The rats were divided into four groups. The rats in Group 1 (n=10) were treated with 30 mg/kg LD_{50} of methamidophos, whereas Group 2 (n=7) was treated with physiologic NaCl equal to the proportion administered to Group 1 via gavage. The animals in Group 1 received no treatment for organophosphate poisoning. Group 2 was designed to serve as the controls for Group 1. Cholinergic symptoms were apparent in the rats in Group 1 in 5 minutes. Eight minutes after ingestion of methamidophos, all of the signs of cholinergic crisis were seen, and the rats were sacrificed. Group 3 (n=10) was given 30 mg/kg LD_{50} of methamidophos via gavage. Time interval until appearance of cholinergic symptoms was the same as in Group 1, i.e., 5 minutes after administering methamidophos. For this group, however, treatment was provided when all of the signs of cholinergic crisis were recorded (after 8 minutes). As the rats in Group 3 developed the symptoms of cholinergic crisis, they were treated with 40 mg/kg 2-PAM IP and atropine IP. Rats in Group 3 received 2-PAM in one dose, but atropine was administered until the cholinergic signs were reversed. The rats in Group 4 (n=7) were treated with physiologic NaCl %0.9 equal to the volume of methamidophos used in Group 3 by means of gavage. In addition, they were given NaCl %0.9, IP in the same number of injections and amount of volume as given in Group 3. The rats in Group 3 received treatment after cholinergic crisis occurred. Group 4 was designed as the control group of Group 3. This design allowed application of the same level of treatment stress in Group 4 as in Group 3. After cholinergic signs were identified in Group 1, intracardiac blood samples were taken from the rats and put into tubes with ethylenediaminetetraacetic acid. Intracardiac blood was drawn from Group 2 after waiting the same amount of time as with Group 1. In Group 3, blood samples were taken after cholinergic signs had disappeared; at the end of the same period, intracardiac blood samples from Group 4 were obtained under anesthesia. The rats were followed for four days in Groups 3 and 4, in order to preclude the intermediate syndrome that is associated with certain compounds 24–96 hours after acute, severe cholinergic crisis. There was no cholingeric crisis observed within the study period.

Statistical analyses were performed using the statistical package SPSS v 10.0. Mann-Whitney U test was used for comparison between groups. Bonferroni's correction was done when multiple comparisons were performed. P values below 0.05 were considered significant. Mean values were presented as ± SD (standard deviation).

Results

The mean level of PCE was significantly lower in Group 1, (32.6±17.0), median: 37.0, range: 45, than in Group 2, (579.4±59.0), median: 595.0, range: 170 (p=0.000). It was significantly higher in Group 3, (392.5±39.4), median: 387.5, range: 130. than in Group 1 (p=0.000). The mean level of PCE was 616.3±54.3 (median: 601.0, range: 141) in Group 4, and was significantly higher than in Group 3 (p=0.000) (Fig. 1). The ultrastructural

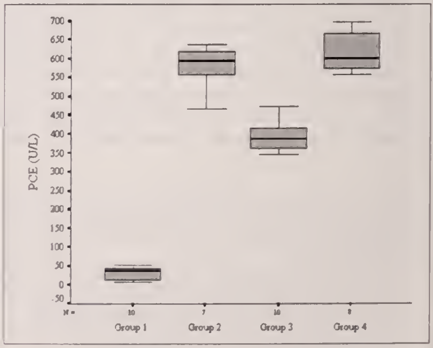

Fig. 1. PCE levels between groups.

changes observed in experiment groups are listed below:

Group 1: Some nuclei of the hepatocytes were irregularly shaped and their chromatin content had increased. Vacuoles were identified in the mitochondria due to lysis of their matrices. In some of the hepatocytes, variously sized lipid droplets were observed throughout the cytoplasm, and glycogen accumulation was also observed in these areas. Increments of collagen fibers, forming bundles, were seen in perisinusoidal spaces (Figs. 2 and 3).

Group 2: The nuclei of the hepatocytes had normal chromatin dispersion and cytoplasmic organelles were normal in structure (Fig. 4).

Group 3: Nuclei of the hepatocytes were regularly outlined and their chromatin content were normal, although cytoplasmic lytic areas were observed in some cells. Overall, cytoplasmic organelles, bile canaliculi and perisinusoidal areas appeared to be normal (Figs. 5 and 6).

Group 4: The cytoplasms and nuclei of the hepatocytes had normal structures. The mitochondria, endoplasmic reticulum cysternae and Golgi apparatus were all within normal limits. Glycogen particles and rare lipid droplets that were the normal structural components of the liver, were also observed (Fig. 7).

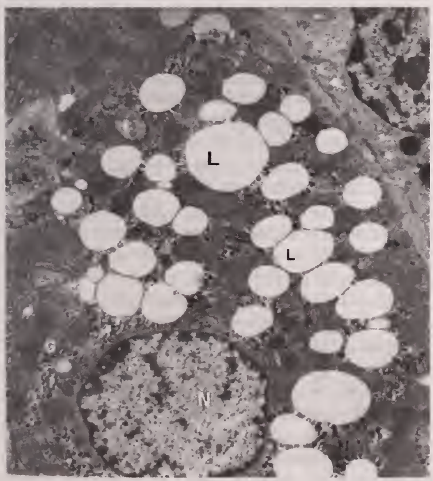

Fig. 2. Increased lipid droplets (L) and glycogen particles (G) are observed throughout the cytoplasm of the hepatocytes of the rat in Group 1. Nucleus (N). (×8837)

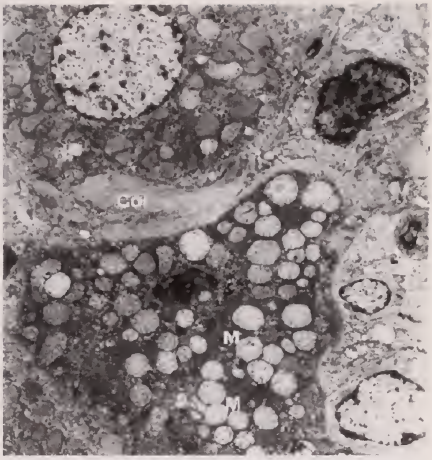

Fig. 3. Lytic mitochondrial matrix (M) appeared in the cytoplasm of hepatocytes of the rats in Group 1. Collagen (Col). (×5512)

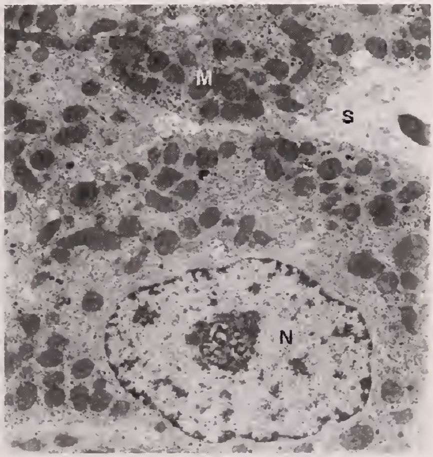

Fig. 4. Nucleus (N) and cytoplasmic organelles are normally seen in the hepatocytes of the rats in Group 2. Mitochondria (M), sinusoidal space (S). (×8837)

Discussion

The liver is involved in about 8% of reported adverse drug reactions. This is a reflection of its central role in the metabolism and excretion of many drugs. A number of drugs may

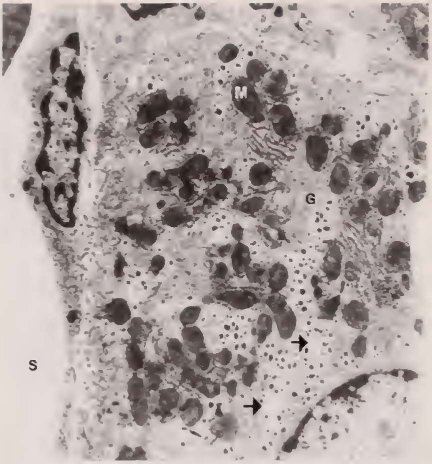

Fig. 5. Mitochondria (M), in variously shaped and small lytic areas (arrows) are seen in the hepatocytes of the rats in Group 3. Glycogen (G), sinusoidal space (S). (×10850)

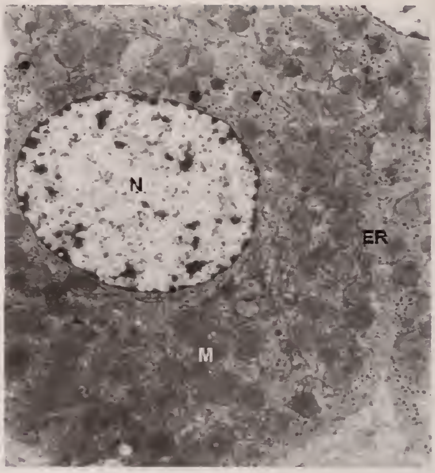

Fig. 7. Mitochondria (M), endoplasmic reticulum cisternae (ER), and nucleus (N) are seen with normal structures in the hepatocytes of the rats in Group 4. (×8837)

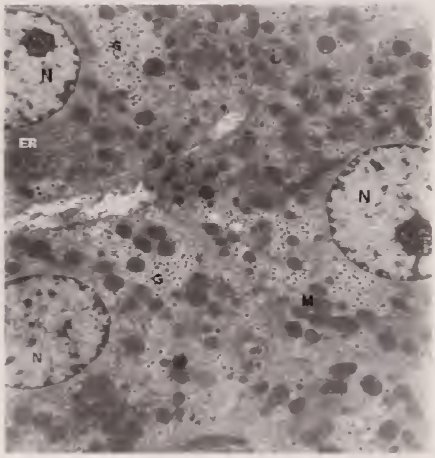

Fig. 6. Nucleus (N), mitochondria (M), endoplasmic reticulum cisternae (ER) and glycogen particles (G) are seen in the hepatocytes of the rats in Group 3. (×7087)

cause induction of the enzymes involved in the metabolism of these drugs (5).

It is well documented that anticholinesterase agents, such as organophosphates, affect lipid metabolism (6–8). Ryhanen et al. showed that low-density lipoprotein and cholesterol contents decreased, whereas high-density lipoprotein concentration increased and very-low-density lipoprotein remained unaffected, in dichlorvos-treated rats. The same study also showed that triglycerides, as well as esterified fatty acids, increased significantly (8). PCE is found mainly in the plasma, and to a lesser extent in the adipose tissue, small intestine, smooth muscle cells and other cells. Clitherow et al. have suggested that PCE may be involved in hepatic and fatty acid metabolism (9). PCE is found to be increased in a significant number of patients with hyperlipoproteinemia (10). It has been suggested that elevation of PCE activity could be attributed to a mechanism leading to an increased secretion rate of lipoproteins (11). Concurrent with the inhibition of PCE activity, levels of serum triglyceride, low-density lipoprotein and glycerol decreased significantly (7). Organophosphates may phosphorylate hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase, which is the major regulatory enzyme in cholesterol biosynthesis. It was found that phosphorylation results in inhibition of this enzyme (12). In our study, following the inhibition of PCE in Group 1, lipid accumulation was remarkable. This finding in Group 1 may be linked directly to the toxic effects of organophosphate and/or distribution of lipid metabolism by the phosphorylation of enzymes in lipid metabolism after poisoning. However, in Group 3, the animals received antidotes after poisoning, and this finding was not observed. This may be because of the temporal relationship between the administering of antidotes and the regeneration of PCE.

It is known that organophosphate insecticides disturb carbohydrate metabolism (13). In organophosphate poisoning, nonketotic hyperglycemia and glycosuria have been reported (14). Signs of organophosphate poisoning may be understood by ascribing them to muscarinic, nicotinic and central nervous system effects. Overstimulation of the nicotinic receptors in the sympathetic ganglia may overwhelm parasympathetic stimulation and produce tachycardia, hypertension, and stimulation of the adrenal medulla (15, 16). The increase in serum glucose is believed to be secondary to the release of catecholamines from adrenal medulla, which is activated by hyperactivity of sympathetic ganglia (17). The accumulation of glycogen in our observations may be attributed to inhibition of glucagon secretion by hyperglycemia and also to the stimulation of liver gluconeogenesis by increased epinephrine secretion. Our findings might also be the result of disruption of carbohydrate metabolism by organophosphates, which was resolved by treatment.

Currently, the precise nature of anticholinesterase-toxicant-induced alterations in liver metabolism has not been clearly ascertained for related organophosphorus toxicants. According to Sitkiewicz, several organophosphates impair respiration and oxidative phosphorylation in liver mitochondrial preparations (18). Rao et al. showed that the total adenosine triphosphatase (ATPase) activity decreased in all tissues, suggesting inhibition of active transport and oxidative phosphorylation under methyl parathion impact (19). Organophosphate intoxication in animals results in mitochondrial swelling, increased proliferation of rough endoplasmic reticulum (RER) and disintegration of smooth endoplasmic reticulum, increased glycogen content and narrowing of biliary pathways. Mitochondrial changes in organophosphate-intoxicated animals are indicative of the increased energy requirements necessary for the cells to overcome the toxic effects of the organophosphorus compound (20). It has also been documented that the increased number of mitochondria in any pathological condition reflects the process of uncoupling of oxidative phosphorylation (21). In contrast, another author has reported that organophosphate intoxication eventuates in actual elevation in hepatocyte metabolic functioning (22). A recent publication showed that organophosphate compounds have cytotoxic effects (23). Mitochondria are primary targets in organophosphate-induced cytotoxicity (24). Our study showed that methamidophos causes damage to mitochondria and nuclei to a lesser extent. The ultrastructural alterations in mitochondria hint at a decrease in mitochondrial energy production, which is probably an important cause of the nuclear changes observed in methamidophos-treated rat liver cells. It is postulated that nuclear changes represent an early proliferative response, whereas cytoplasmic changes reflect the disruption of normal function and hepatotoxic injury (6).

With most forms of injury, in addition to loss of specialized cells, the surrounding matrix of connective tissue is damaged. The fibroblasts synthesize and secrete fibronectin and proteoglycans, and these form the scaffolding for rebuilding the matrix (25). In our study, the collagen fiber increment in Group 1 may be due to injury of hepatocytes because of acute intoxication by organophosphate. After treatment (in Group 3), these ultrastructural changes disappeared, since the induction due to injury stopped with the administration of antidotes. The collagen fiber increment in Group 1 might also have occurred because of lipid accumulation. The fat-storing cells exhibited intense positive stainings for type I and type III collagens and prolyl hydroxylase (26). It has been showed that prolyl hydroxylase plays an important role in collagen fiber development (27). Hepatocyte injury resulting from acute exposure to organophosphate compounds, alterations in prolyl hydroxylase enzyme activity following lipid accumulation, and its return to normal limits after treatment, may be causes of collagen fiber increment in Group 1 and its absence in Group 3.

A drawback of the present study was the time interval between the occurrence and the disappearance of the ultrastructural changes in Group 3, since the disappearance of the ultrastructural changes might be related to time factors. Indeed, it is obvious that the metabolism rate in rats is very fast (relative to humans) and the healing of these changes might be due to this factor. But it must also be noted that the effect of time factor in this study has been alleviated by designing another group.

In regard to ultrastructural changes, hepatocytes exposed to highly toxic organophosphate were seriously affected, but after an appropriately tailored treatment these changes disappeared. Deaths following this kind of poisoning may be linked to the morphological alterations in the liver and the detoxification factory of the body. Further studies are needed to clarify these causal relationships.

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Book Reviews

Cardiac Pacemakers Step by Step: An Illustrated Guide

S. Serge Barold, Roland X. Stroobandt, and Alfons F. Sinnaeve. Elmsford, NY: Blackwell Publishing; 2004. 341 pp. $55.00. ISBN: 1-4051-1647-1.

Dr. Barold, a Mount Sinai alumnus, and his colleagues have produced an effective tool for those seeking to learn basic concepts about cardiac pacemakers. The book is geared towards a wide range of learners, from beginners to advanced users of pacing devices including medical students, residents, cardiology fellows, cardiac electrophysiology fellows, implanting surgeons, nurses, sales representatives and anyone who wishes to rapidly gain a comprehensive understanding. It represents a particularly useful alternative for beginners who might be intimidated by less manageable texts on the subject.

Initial chapters present introductory aspects of electrocardiography and electrical impulses as applicable to pacemaker functions. Subsequent chapters clarify basic and advanced concepts in cardiac pacing as applicable to bradycardia and anti-tachycardia pacemakers. The method is also applicable to the same functions in implantable-defibrillators. The final chapters deal with complex problems with pacemakers, such as under- and over-sensing, pacemaker-mediated tachycardias and pacemaker failure.

With almost 300 pages containing color diagrams, the book is sure to appeal to those who benefit from visual aids and dislike reading large tracts of text. Alfons F. Sinnaeve must be complimented on the clarity with which he has visually presented basic as well as advanced concepts in cardiac pacemakers. Both basic pacing concepts (fundamentals of electricity, normal pacemaker function, electrocardiograms, and radiography) and advanced concepts (pacemaker malfunction, rate response, automatic mode switch, hysteresis, pacemaker-mediated tachycardia, biventricular pacing, and trouble shooting) are clearly presented. While there are the inevitable minor errors in spelling and syntax often found in a first edition text, on the whole this is a comprehensive book that will make a valuable addition to any medical library.

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Peripheral Vascular Disease for Cardiologists. A Clinical Approach

John A. Spittell. Elmsford, NY: Futura, Blackwell Publishing; 2004. 134 pp. $54.95. ISBN: 1-4051-0366-3

With the growing rate of diabetes mellitus, obesity, and the metabolic syndrome in our population, cardiologists are paying more attention to the increasing burden of atherosclerosis. Yet in cardiology fellowship training, the common focus in the areas of heart failure, arrhythmia, and primary prevention has been the detection and treatment of underlying coronary artery disease. With so much attention directed to heart and coronary artery disease, cardiologists and fellows-in-training often do not obtain the skills necessary to identify and treat peripheral vascular disease. According to the recent national cross-sectional survey of Peripheral arterial disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS), more than 70% of primary care providers whose patients were screened for this study were unaware of the presence of peripheral arterial disease (PAD) in their patients.

In *Peripheral Vascular Disease for Cardiologists*, Dr. John Spittell describes a wide spectrum of both atherosclerotic and non-atherosclerotic vascular diseases. In addition to PAD, Dr. Spittell discusses a range of topics in peripheral vascular disease, from diseases of the aorta to venous disorders. His intention in writing this book was "to broaden the knowledge base and clinical skills in the recognition and management of common peripheral vascular disorders that occur in cardiologic practice." As stated in the foreword by Dr. Valentin Fuster, Dr. Spittell has had vast clinical experience in the area of peripheral vascular disease and "has done more to encourage involvement of the cardiovascular community in peripheral vascular disease than any other individual I know."

Dr. Spittell provides a helpful overview of vascular disease processes that are likely to be seen in any cardiology and primary care practice. But the strongest feature of this book is its author's emphasis on basics: a complete history, physical examination, and peripheral vascular assessment, especially for high-risk patients with either established coronary artery disease or cardiac risk factors. In current cardiology fellowship training, the focus is on learning the latest technology and tools for diagnosing diseases, with not enough emphasis on the importance and value of a thorough physical examination. Dr. Spittell reacquaints us with basic and advanced physical maneuvers and signs for diagnosing a number of vascular disease processes. For example, the ankle-brachial index (ABI), described in the book, is a simple noninvasive technique that can be performed in any office setting. "The ABI has become the objective standard for [PAD] diagnosis." It might have been useful to provide the reader with values for normal and abnormal ABIs.

Through the rest of the book, Dr. Spittell covers topics such as aortic dissection, aneurysm, arteritis, vasospastic disorders, venous disorders, and leg and foot ulcers. To accompany each vascular disease topic, he provides excellent images of physical and radiographic findings, and of gross pathology, to illustrate the manifestations of particular vascular disorders. In the next to last chapter, Dr. Spittell describes physical findings used as reliable "shortcuts" to different vascular diagnoses. For example, he illustrates physical manifestations of infective endocarditis (Roth spots, splinter hemorrhages, Osler's nodes) and Osler-Weber-Rendu disease (finger telangiectasias). In the final chapter, he provides an excellent discussion on "uncommon peripheral vascular disorders," such as thoracic outlet syndrome and occlusive arterial disease in the hand due to blunt trauma.

Although Dr. Spittell covers a wide spectrum of vascular diseases, he does not discuss the management of PAD in sufficient detail to reflect the current standard of practice. In describing the management of PAD, he simply states that "in an effort to delay progression of atherosclerosis attention to the controllable risk factors—smoking, diabetes mellitus, hyperlipidemia, and hypertension—is basic." Dr. Spittell fails to mention that specific types of medication such as angiotensin-converting enzyme (ACE) inhibitors and statins are particularly beneficial for PAD patients. The morbidity and mortality impact that ACE inhibitors and statins have on PAD patients are independent of the risk factor benefits, based on the Hope Outcomes Prevention Evaluation (HOPE) and Heart Protection studies, respectively. It is currently accepted that PAD is a coronary heart disease equivalent and should be (aggressively) treated accordingly.

Dr. Spittell provides a review of peripheral vascular disease processes and discusses the means to examine, test and treat these disorders. His book provides an excellent synopsis of various vascular diseases and a thorough overview of their diagnostic histories. However, it does not cover in sufficient detail the rapid advances that have been made in imaging and therapy for many common vascular diseases, such as PAD. Although intended for cardiologists, this book can surely benefit primary care physicians, fellows-in-training, residents, and medical students. Disorders such as PAD are becoming increasing prevalent, yet continue to be underdiagnosed and undertreated. This book provides insight into the manifestations of peripheral vascular disease and stresses the need for clinicians to be skilled in examining, evaluating and appropriately treating patients who develop these diseases.

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Health Literacy: A Prescription to End Confusion

Lynn Nielsen-Bohlman, Allison Panzer, David Kindig, editors. Washington, DC: The National Academies Press. 2004. 345 pp., index. $47.95. ISBN: 0-309-09117-9.

THE BOARD OF NEUROSCIENCE and Behavioral Health of the Institute of Medicine of the National Academies was concerned about the apparent lack of health literacy of the general public. Many health professionals and policy makers seem to be unaware of the extent and effect of such illiteracy. The book was written, by a panel of experts, to analyze and clarify this problem and suggest some possible solutions.

The book carefully documents the following factors in health literacy and illiteracy: (a) health literacy correlates with the general literacy and level of education of various socioeconomic groups; (b) the elderly have a diminishing capacity to understand medical information and (partly as a result) to obtain appropriate health care; (c) people with less education tend to get less (and less appropriate) medical treatment than those who are better educated; (d) many medical forms are difficult to complete and tend to confuse patients to some degree; (e) decisions for health care providers are regularly made by personnel with minimum training in medicine; and (f) most national studies with specific recommendations for improving life styles or preventing disease are not implemented by the public.

This book has both strengths and weaknesses. Each chapter is well referenced, but most of the case illustrations are worst-case scenarios and the algorithms and tables tend to be boring and unhelpful. The problems with health literacy are well defined, but an overall prescription to end the confusion is never quite filled.

The work of previous committees and regional studies on health literacy is thoroughly described. And the book presents a number of pragmatic suggestions for newer committees and health care administrators to implement. It is not written for the lay public or the average practitioner, but rather for policy makers and committees trying to make health care forms and authorization documents more understandable, to implement national studies, and to improve health literacy for senior citizens as well as for economically and socially disadvantaged adults. As such, it at least represents several important steps in the right direction.

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Pharmacy Law Digest, 39th Edition

Joseph L. Fink III, Jesse C. Vivian, and Ilisa B.G. Bernstein. Saint Louis, MO: Facts and Comparisons, part of Wolters Kluwer Health; 2004. 1,024 pp. $62.95. ISBN: 1-57439-202-6.

THE 39TH EDITION OF *Pharmacy Law Digest* is an approximately 1,000-page compilation of pharmacy-related legal issues. The introductory chapter provides general information about the basic types of law (i.e., statutes and regulations), the organization of the judicial system (federal and state courts) and differences in trial procedures (i.e., civil and criminal courts). In addition, the first chapter explains where the law can be found and how to read it.

The next chapter describes in detail the federal Food, Drug and Cosmetic (FD & C) Act, which is the main body of law related to regulation of pharmaceuticals. The history of and various amendments to the FD & C Act are chronicled, and each requirement of the Act is detailed and explained. The importing and exporting of drugs, a topic of recent controversy and debate, is described. Further, the text explains FD & C rules and regulations surrounding the compounding, labeling, dispensing, repackaging and shipping/mailing of pharmaceuticals. Also covered are the FD & C regulations on the marketing of pharmaceuticals and "direct-to-consumer" advertising.

Although the book's presentation of federal rules and regulations is detailed and systematic, it does not (and probably could not) provide the same type of information for state law. Yet many legal aspects of pharmacy practice are determined by state law. Therefore, readers/practitioners are often referred to their particular state law to determine the legality of a particular issue.

The entire third chapter is dedicated to the Controlled Substances Act, the principal federal law regulating such drugs. The chapter reviews the meaning of each of the schedules, proper labeling practices, procedures for ordering, and record-keeping requirements for controlled substances. Federal rules for prescribing and dispensing controlled drugs, as well as procedures for disposal of excess controlled drugs are presented.

The fourth chapter is about pharmacy inspection by various regulatory agencies (FDA, DEA or municipal agencies). It is a useful section for those individuals who own or operate their own pharmacies, as well as for those in institutional practice who are responsible for regulatory compliance. The chapter also includes useful "Do's and Don't's" for the practitioner faced with a regulatory inspection.

There is also a chapter in the book dedicated to business law. It defines many legal terms related to this topic. The subsection on contract law reviews the fundamentals of contracts and provides the legal meanings of key terms. The subsection on employment law reviews various types of discrimination (e.g., age or gender) and sexual harassment. This chapter of the book is especially useful for the proprietor-pharmacist who may not have knowledge in this area.

The main body of the book contains summaries of hundreds of actual lawsuits. The summaries are about 1 – 1 1/2 pages long. Each case is broken down into four sections. "ISSUE" describes, in one or two sentences, what the dispute was about. "FACTS" is a section several paragraphs long that describes the chronological chain of events in the case. "RULING" is a one-paragraph section stating how the court ruled and "REASONING" explains how the law was applied to the facts of the case and the court's interpretation of the law. This section is by far the largest in the book and the most interesting, in that the interpretation and spirit of the law is explained. The cases are sorted into subsections within the chapter, by category. For example, all lawsuits related to drug-drug interactions, dispensing, failure to warn (among many others) are grouped together. The latest edition has cases as recent as 2003, as well as many older court cases.

At the end of each of the chapters there are multiple-choice study questions, critical thinking scenarios and case studies to help reinforce and highlight the most salient points of that section (answer keys are also provided, including the rationale for the correct choices).

A useful index of key drug and licensing laws and how they differ from state to state is provided. The 39th edition represents a minor revision as compared with the previous edition. Some of the revisions in the new edition include an updated review of the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996, changes to the Pediatric Research Equity Act, and the latest on Medicare legislation.

The target audience for this book includes prescribers, pharmacists, pharmacy students and pharmacy technicians. The book appears to be factually correct and is laid out in a logical format that explains the subject matter in a simple, easy-to-understand manner.

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Abstracts

The following abstracts were presented by investigators at the Twentieth Annual Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine Research Evening on June 4, 2004, at the New York Academy of Medicine. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as the Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Abstracts from Queens Hospital Center and Jersey City Medical Center were presented as posters on Research Day, held on May 26, 2004, at both institutions.

Research in Medicine 2004
Mount Sinai School of Medicine

Basic Research

Neovascularization, Inflammation and Intra-Plaque Hemorrhage are Increased in Advanced Human Atherosclerosis from Patients with Diabetes Mellitus. K.-R. Purushothaman[1], D. Echeverri[2], V. Fuster[1], W.N. O'Connor[2], J.J. Badimon[1], and P.R. Moreno[1,2]. [1]Mount Sinai Medical Center, New York, NY, and [2]University of Kentucky, Lexington, KY.

Background: Neovascularization, a process associated with inflammation and plaque hemorrhage, may play a role in the pathophysiology of diabetic atherosclerosis.

Hypothesis: We hypothesize that diabetic atherosclerotic lesions have increased neovessel content with higher inflammation and intra-plaque hemorrhage compared to non-diabetic atherosclerotic lesions.

Materials and Methods: Neovascularization, inflammation and hemorrhage were evaluated in 125 Type II diabetic and 105 non-diabetic human aortic plaques obtained at the time of autopsy. Neovessel content and Macrophages/T lymphocyte cells (macs/T cells) were identified by double immunochemistry labeling for CD34 and CD68/CD3 respectively in the intima and by CD34/alpha-actin in the media respectively. Macs/T cells were counted within the fibrous cap and shoulder regions and scored 0 ($\leq$ 5 cells), 1 ($\geq$ 6–25 cells), and 2 ($\geq$ 25 cells). Intra-plaque hemorrhage was identified in Hematoxylin and Eosin stain as dense erythrocyte extravasation and fibrin deposition within the lipid core. Neovessel content was manually counted within outer, inner media, intima and fibrous cap/shoulder.

Results:

	Non-Diabetes (N01-5)	Diabetes (n=125)	p value
Neovessels (outer media)	81±4	142±5	0.0001
Neovessels (inner media)	32±2	85±5	0.0001
Neovessels (intima)	7±0.7	21±5	0.0001
Macs/Tcells(Fibrous Cap)	0.9±0.1	1.4±0.1	0.0001
Macs/Tcells(Shoulder)	1.4±0.07	1.7±0.1	0.0001
Intra-plaque hemorrhage	17%	42%	0.0001

Multiple logistic regression analysis identified intimal neovascularization as the only independent predictor for intra-plaque hemorrhage (RR=1.12; 95% CI=1.04–1.2; p=0.001).

Conclusions: Diabetic atherosclerotic lesions have increased neovessel content with higher inflammation and intra-plaque hemorrhage compared to non-diabetic atherosclerotic lesions, suggesting a role for neovascularization in the pathophysiology of diabetic atherosclerosis.

In Vivo Caspase-Inhibition Prevents Plaque Progression by Reducing Apoptosis and Tissue-Factor Expression in a Mouse Model of Chronic Atherosclerosis. R. Hutter[1], C. Valdiviezo[1], B. Sauter[2], G. Panjrath[1], F. Carrick[2], V. Fuster[1], and J.J. Badimon[1]. [1]The Cardiovascular Institute and [2]Division of Gastroenterology, Mount Sinai Medical Center, New York, NY.

Background: Lipid lowering therapy has been shown to reduce thrombogenicity of atherosclerotic plaques. Inflammatory cells undergoing apoptosis when exposed to ox-LDL in lipid-rich plaque can contribute to plaque thrombogenicity via synthesis and secretion of tissue-factor (TF). Therefore, increased intimal apoptosis and tissue-factor expression could be a key factor for accelerating plaque progression. To test this hypothesis we evaluated the effect of caspase-inhibition (CI) on plaque size, intravascular lipid deposition and intimal expression of active-caspase-3 (aCS) and TF in a mouse model of atherosclerosis *in vivo*.

Methods: Apo-E -/- mice (n=13) were fed a Western Diet for 7 months. Three animals were sacrificed at 7 months and served as baseline control group (BL). Ten animals were randomized into treatment (TR) (n=5) and control group (CT) (n=5) receiving either 3 weeks of continuous CI treatment (daily i.p. injection of 30 mg/kg of Q-VD-OPH general caspase-inhibitor in 50 mcl DMSO, Enzyme Systems, CA) (n=5) or DMSO treatment alone (n=5) (all data as mean±SEM). Plasma cholesterol levels were similar in all groups with 780±58mg/dL for the BSL group, and 958±64 mg/dL and 854±56 mg/dL for the TR and CT group, respectively. Atherosclerotic disease burden was assessed by (immuno)histo-morphometric analysis of the aortic root and by Sudan IV fat stainings of whole-mounted abdominal aorta.

Results: CI treatment significantly reduced plaque size at the aortic root level compared to controls (0.59±0.05 vs. 0.88±0.04, $P<0.01$). When compared to baseline there was no significant difference in plaque size with CI treatment. Sudan IV staining of abdominal aorta was significantly reduced by CI treatment compared to CT and BSL. In aortic root atherosclerotic plaques, both aCS-3 and TF protein expression were significantly reduced by CI treatment compared to CT and BSL (aCS3: 9%±2 *vs.* 30%±3, $P<0.01$; 9%±2 vs. 23%±3, $P<0.01$, respectively; TF: 15%±2 vs. 41%±3, $P<0.01$; 15%±2 vs. 43%±5, $P<0.01$, respectively) and correlated positively with plaque size ($P<0.05$). Double-labeling demonstrated a strong co-localization of TF and aCS-3 antigen.

Conclusion*:* CI treatment clearly prevented plaque progression and reversed the increased intimal expression of both apoptosis and TF despite persistently elevated blood lipid levels. These findings point to intimal apoptosis and associated tissue-factor expression as a possible final common pathway involved in plaque progression. Therefore, reduction of intimal apoptosis by caspase-inhibitors could become a powerful tool to protect intimal cells from diverse pro-apoptotic stimuli/risk factors and could lead to a better treatment of atherosclerotic disease progression.

The VPAC$_1$ Receptor: A Molecular Target for Breast Cancer Diagnosis and Treatment? J.M. Mehnert and M. Babyatsky. Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Aim: To examine the putative role of the VPAC$_1$ receptor in the targeted delivery of radionuclides and therapeutic agents in breast cancer as set forth in the scientific literature.

Background: Vasoactive Intestinal Peptide is a neurotransmitter that also functions as a trophic factor in embryogenesis, the central nervous system and the gastrointestinal tract. Three types of VIP receptors have been cloned including VPAC$_1$ VPAC$_2$ and the pituitary adenylate cyclase activating polypeptide (PACAP) receptor.

Findings: *In vitro* autoradiography studies demonstrate that the great majority of human tumors, including breast, prostate, colorectal and lung, express the VPAC$_1$ receptor. mRNA for the VPAC$_1$ receptor has been detected in breast cell lines using Northern blot analysis and RT-PCR techniques. VIP antagonists inhibit specific VIP binding in breast cancer cell lines, decrease the ability of VIP to elevate cAMP and c-fos mRNA, and potentiate the effects of chemotherapeutic agents in breast cancer cell lines and in mice bearing xenografts. VIP modified and labeled with technetium-99 localized breast tumors in rats and humans.

Conclusions: The VPAC$_1$ receptor, expressed in both normal and neoplastic breast tissue, may be a potentially useful target in the early identification and treatment of breast cancer. The available data suggest that VIP agonists may be used for the targeted imaging of breast cancer, and

VIP antagonists may inhibit neoplastic cell growth and potentiate chemotherapeutic drugs *in vitro*.

Evidence for Hypoxia and HIF-1-alpha Mediated VEGF Expression in Lipid-Rich Plaque Macrophages as Link between Inflammation and Angiogenesis. R. Hutter[1], B. Sauter[2], C. Valdiviezo[1], F. Carrick[1], J.T. Fallon[1], V. Fuster , and J.J. Badimon[1]. [1]The Cardiovascular Institute and [2]Division of Gastroenterology, Mount Sinai Medical Center, New York, NY.

Background: Macrophages expressing the pro-angiogenic factor VEGF in lipid-rich plaque are considered to contribute to plaque progression and vulnerability *via* induction of intimal neovascularization. Hypoxia Inducible Factor 1-alpha (HIF-1 alpha) has been identified as key transcriptional regulator of cellular VEGF-synthesis and mediates the angiogenic response of tissues to hypoxia. However, little is known on the pattern of expression of HIF-1 alpha in macrophages of atherosclerotic lesions and its relation to plaque lipid content. Our objective was to assess the expression of HIF-1 alpha and VEGF in human and experimental atherosclerosis comparing lipid-rich plaque macrophages with fibrous plaque cells.

Methods: In human carotid and coronary atherosclerotic lesions (n=12) HIF-1 alpha and VEGF mRNA and protein expression was evaluated by in situ hybridization and immunohistochemistry (data presented as mean percentage of intimal cells positive for HIF-1 alpha or VEGF, ± SEM). In New Zealand white rabbits (n=14) atherosclerotic lesions were induced by the combination of aortic double balloon injury and 9 months of high-cholesterol (HC) diet. Five rabbits were sacrificed at 9 months and were used as baseline (BL). The remaining rabbits were then randomized into continued HC diet (n=5, progression group) and normal chow diet (ND) (n=4, regression group) for another 6 months. A significant hypolipidemic effect was introduced by resuming ND diet at 9 months. Total serum cholesterol at the end of ND treatment was 27±10 mg/mL vs. 861±143 mg/mL at BL ($P<0.01$) and 526±108 mg/mL with continued HC-diet at 15 months ($P<0.01$).

Results: In human atheroma, HIF-1 alpha and VEGF mRNA and protein expression were selectively increased in lipid-rich compared to fibrous plaque components (23±5% vs. 5±2%, $P<0.01$; 32±6% vs. 8±3%, $P<0.05$, respectively) and correlated with high macrophage content ($P<0.05$). In addition, intimal neovascularization was significantly increased in lipid-rich compared to fibrous plaque areas ($P<0.05$). Double-labeling studies demonstrated a strong co-localization of HIF-1 alpha and VEGF antigen in inflammatory cells surrounding intimal neovessels in close proximity to cholesterol clefts. In atherosclerotic lesions of rabbits with continued HC diet and high serum lipid levels expression of both HIF-1 alpha and VEGF-protein as assessed by immunohistochemistry and Western Blot was dramatically and significantly increased compared to baseline and compared to regression group.

Conclusions: The selective expression of HIF-1 alpha in VEGF-positive macrophages located in lipid-rich plaque tissue of human and experimental atherosclerosis points to hypoxia as possible link between lipid-related inflammation and angiogenesis. Both processes might synergistically contribute to plaque progression and vulnerability.

Clinical Research

Visiting Doctors. 3rd Year Creative Project Description. A. Blohm. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

My third year academic project is an offspring of the "creative project" that was required at the end of our visiting doctor's month. At that time I photographed one of my IMA patients in her home and was both maddened and fascinated by the resulting portrait: a diabetic woman with amputated toes sharing her bed with bottles of prescription medicine and a shoebox full of cigarettes. It was the Portrait of my Frustration, and it made me realize that as long as I continued to see this person as only "a patient" I was never going to win at the senseless game of saving her from herself.

I wanted to continue to examine this issue, and with the collaboration of the Visiting Doctor's Program I began to photograph homebound patients. I tried to understand and capture the experience of those who are chronically ill, the frustration, denial, acceptance, isolation, hurdles, pain, hope, humor, and most importantly, the adjustments that people make in their lives when medical illness forces them to remove themselves from the outside world. Do they become prisoners in their own home or Kings and Queens of their Manhattan apartment?

Part-way through the project I was so moved by what these people were telling me that I also began to digitally record patients' thoughts and observations about their illness experience. I combined the pictures and the stories, and although I do not have a poster or an abstract, I do have a slide show with voice-over that when fully edited will be approximately ten minutes long.

I have run into several obstacles, most importantly the issue of breaching doctor-patient confidentiality and obtaining genuine informed consent to use the photographs in a public setting. These definitely merit further consideration, and I plan to make this part of my academic work in the future.

Topical Tacrolimus Alcohol Induced Flush Presenting as Food Allergy. A.K. Knight and M.J. Chandler. Mount Sinai School of Medicine, New York, NY.

Introduction: Topical treatment with tacrolimus may be complicated by ingestion related flushing after consuming small amounts of alcohol that can be mistaken for food allergy.

Methods: A patient with a history of allergic rhinitis, atopic dermatitis, oral allergy syndrome and fish anaphylaxis was evaluated for ingestion related facial eruptions which began shortly after instituting topical tacrolimus to his peri-oral and peri-orbital eczema. Food allergy was first thought to be the problem with beer the most frequent trigger.

Results: Over time, it became clear that alcohols, including neutral spirits like vodka, were also implicated. An in-office challenge was done with less than 1 ounce of white wine. Within 2–3 minutes of ingestion, there appeared an intense, non-pruritic erythema restricted to the areas of applied tacrolimus in a peri-oral and peri-orbital distribution. In discussions with Fujisawa (maker of Protopic brand of topical tacrolimus) they acknowledged receiving other anecdotal reports of topical tacrolimus related alcohol flushing. On this basis tacrolimus use was discontinued and within 2 weeks, the alcohol flush reaction disappeared but the eczema returned. Since the initial case presentation, two more patients with similar stories and response to tacrolimus cessation were seen.

Conclusions: A careful history including alcohol use should be obtained from patients who use topical tacrolimus presenting with new skin complaints, as these may be evidence of an avoidable drug interaction and not worsening of atopic disease or an additional food allergy.

Prescription Costs in an Urban Homebound Population. I.M. Kronish[1] and J. Boal[1,2]. Departments of [1]Medicine and [2]Geriatrics, Mount Sinai School of Medicine, New York, NY.

Introduction: Little is known about the cost of prescriptions in the growing population of homebound adults. The goal of this paper is to measure the cost of prescriptions in a cohort of homebound and to assess whether these costs are associated with measures of disease burden, functional status, and insurance status.

Methods: We retrospectively surveyed 417 patients enrolled in an urban primary care program for the homebound between September 1996 and October 2002. Patients were eligible if they met the Medicare definition of homebound and resided in Manhattan. Information was collected pertaining to patient demographics, functional status, and Charlson score. Prescription costs were calculated according to the average wholesale drug price.

Results: A total of 415 homebound patients, ages 25–106 (median 83, interquartile range (IQ) 75–91), had an average monthly cost of prescriptions of $350 SD $365 (range $1–$3355). Their median cost was $254 IQ $150–$443. These patients were taking 10.8 SD 4.8 medications per month (range 1–27). Multivariate analysis showed that age was inversely associated with costs ($P<0.001$). ADL score, a measure of functional status, was not significantly associated with prescription costs. Charlson score, a measure of disease burden, was highly correlated with cost ($P<0.001$). 26% of patients in the sample had no prescription drug coverage. Their costs remained high: $277 SD $247 per month. In multivariate analysis, the presence or absence of prescription coverage did not predict prescription costs.

Conclusions: Urban homebound patients represent a special group with respect to increased burden of disease and elevated prescription drug costs. Disease burden rather than functional status is significantly correlated with prescription drug costs. A significant portion of homebound patients lack prescription insurance. Extension of prescription coverage to self-paying members of this group will not likely lead to an increase in their prescription costs.

Do National Football League Players Have Increased Left Ventricular Mass? L.B. Croft[1], A. Nair[1], A. Roberts[2], and M. Goldman[1]. [1]Mount Sinai Hospital, New York, NY, and [2]Living Heart Foundation, Little Silver, NJ.

Introduction: A recent study of selected National Football League (NFL) players reported an increased left ventricular mass (LVM) and wall thickness (WT) which correlated with weight and body surface area (BSA).

Objective: To confirm that football players have increased LVM and WT that is exaggerated in linemen (LM) vs. non-linemen (position players (PP)).

Methods: We performed 2-D echo studies (Cypress, Siemens) on non-selected NFL football players during a pilot study. WT and LV diastolic internal diameter (LVID) were measured. LVM was calculated from 2-D. Resting blood pressure (average of 3 readings) and electrocardiograms (ECG) were obtained. Players were divided into 2 groups: LM and PP.

Results: Mean age was 25 ± 3 years; height (ht) = 1.9 ± 0.06 m; weight=112.2 ± 18 kg. LVM corrected for height correlated with systolic blood pressure ($R=0.45$, $p=0.04$) but not body surface area or weight. When the LM with hypertension (systolic >140 mm HG) was excluded, no player had increased LVM/height. Twenty-nine percent had ECG evidence of LV hypertrophy. However, none of these players had echo evidence of increased LVM. Five out of six patients with LV hypertrophy by ECG were in PP, while the LM with true LVH had normal ECGs.

Conclusion: In this pilot study, NFL football players did not have increased LVM when corrected for height, but increased mass did correlate with systolic blood pressure. ECG was not an effective screening tool for LVM. Players may have benefited from improved training techniques and healthy lifestyles as reflected in better cardiac remodeling than previously seen.

A Comparison of Morning Blood Pressure Surge in Blacks and Whites. D.C. Haas[1], L.M. Gerber[2], J.E. Schwartz[3], K. Warren[2], A. Nair[1], and T.G. Pickering[4]. [1]Mount Sinai Hospital and [2]Cornell Medical College, New York, NY; [3]Stony Brook University, Stony Brook, NY; and [4]Columbia University Medical Center, New York, NY.

Introduction: Blacks have twice the lifetime risk of suffering a stroke compared to whites; however the reasons for this disparity have yet to be fully elucidated. A recent study among elderly Japanese hypertensives suggests that morning blood pressure surge (MBPS) is an independent predictor of cerebrovascular disease. Therefore, since MBPS may be an important determinant of cerebrovascular disease, we tested whether blacks and whites differed with respect to MBPS.

Methods: 122 blacks (35% men) and 103 whites (50% men), age 18–65, enrolled in a cross-sectional study of race, socioeconomic status and cardiovascular disease were analyzed. Ambulatory BP monitoring (ABPM) for 24 hours was performed. Treated hypertensive subjects were off medication for at least two weeks before ABPM. MBPS was defined as morning BP (average systolic BP (SBP) during the first 2 awake hours) minus the trough BP during sleep (lowest value of the 5-point moving average of successive sleep SBP readings). Percentage nocturnal SBP reduction ("dipping") was calculated [100 × (1- mean sleep SBP/mean awake SBP)] and subjects sub-classified: extreme dippers ($\geq 20\%$), dippers (10–19%), non-dippers (0–9%), and risers (less than 0%).

Results: Compared to whites, blacks had similar awake SBP (135 vs. 133 mm Hg, $p>0.20$), but higher sleep SBP (123 vs. 115 mm Hg, $p<0.002$); they were also somewhat younger (45y vs. 48y, $p<0.02$) and heavier (BMI: 30 vs. 28 kg/m^2, $p<0.03$). The MBPS averaged 21 mmHg in blacks and vs. 25 mm Hg in whites ($p<0.02$). Adjusting for gender, age, and BMI, the average MBPS for blacks was 22 mm Hg compared to 25 in whites ($p=0.06$). In the fully adjusted model, including dipping status, the average MBPS for blacks was 21 mmHg compared to 22 in whites ($p>0.50$).

Conclusions: In this non-elderly U.S. sample, blacks have a significantly lower MBPS than whites. This difference can be almost entirely accounted for by differences in gender, age, BMI, and dipping status. This finding suggests that MBPS is unlikely to account for black/white differences in stroke incidence.

Tolerability of Long-Term Intravenous Milrinone. D.A. Baran[1,2] and D.A. Reynolds[1]. [1]Mount Sinai School of Medicine, New York, NY, and [2]Newark Beth Israel Medical Center, Newark, NJ.

Introduction: Milrinone is a phosphodiesterase inhibitor that has been shown to have short-term benefit for individuals with heart failure. However, there has been concern over increased risk of adverse events, specifically arrhythmogenicity and hypotension, with extended usage. This study retrospectively assesses the tolerability of extended use intravenous milrinone in hospitalized patients. Multiple patient characteristics were examined to identify characteristics that may be associated with an increased risk of an adverse outcome.

Methods: Retrospectively analyzed charts from 178 patients admitted for milrinone therapy from January 1996 to December 1999 using an inpatient pharmacy drug utilization database. All adult patients on milrinone for more than twenty-four hours were included. Specific patient demographics and cardiac history were abstracted. Adverse events were defined as: any new arrhythmia, hemodynamically significant hypotension, death or other adverse events that required discontinuation of milrinone. Additional severe adverse events were defined as need for IABP, defibrillation or ICD placement for arrhythmia. Outcomes included discharge from the hospital, cardiac transplantation and death.

Results: The rate of non-sustained ventricular tachycardia was increased in patients on long-term milrinone therapy. However, the rate of serious adverse events was not increased in patients on long-term therapy. Etiology of heart failure, history of cardiac risk factors, and prior use of anti-arrhythmic therapy were not correlated with an adverse event on therapy. Sepsis was a major cause of death.

Conclusion: Milrinone administered over an extended length of time in an inpatient setting is well tolerated. There was no significant correlation for an adverse event in patients with reduced creatinine clearance. Careful monitoring of electrolytes and titrating the dose of milrinone when non-sustained ventricular tachycardia was observed may have prevented development of an adverse outcome.

Value of the Epworth Sleepiness Scale (ESS, a Questionnaire) as a Screening Tool Either Alone or in Combination with Obesity and Snoring as a Screen for Sleep Disorders. T.M. Azam, J. Chronakos, R. Waldman, S.J. Wieber. Department of Pulmonary Critical Care and Sleep Medicine, Mount Sinai School of Medicine, New York, NY.

Excessive daytime somnolence (EDS) is often a presenting symptom for sleep-disordered breathing (SDB). Although SDB affects an estimated 2–4% of the adult population, it is an underrecognized disorder whose true incidence is not known. Despite its prevalence, recent studies have shown that primary care physicians referred less than 1 percent of their patient panels for evaluation of SDB, thus under-diagnosing those with SDB. This low referral rate was attributed to multiple factors, such as limited formal training in this area and a shortage of sleep specialists available for consultation. The lack of a good screening test for patients with SDB has also been an often-cited reason for underdiagnosis.

The Epworth Sleepiness Scale (ESS) is a self-administered eight-item questionnaire that was initially published in 1991 as a measure of excessive daytime sleepiness (EDS) and was subsequently validated as a good screening test for SDB. However, more recent studies have challenged these results. Chervin et al. reported no correlation between ESS and SDB as measured by NPSG. Other criteria, such as BMI, presence of habitual snoring, neck circumference, hypertension, and bed partner's report of nocturnal gasping/choking have been also suggested as reliable clinical predictors of SDB.

The Department of Pulmonary Medicine of The Mount Sinai School of Medicine has begun to administer a screening questionnaire consisting of the ESS as well as questions about height and weight and the presence or absence of snoring as part of routine care to patients seen in both a pulmonary specialty and primary care faculty practice. Patients with an ESS score of 9 or greater or patients with a body mass index (BMI) greater than 25 who snore have been referred to the Mount Sinai Hospital Sleep Center, where they have undergone overnight nocturnal polysomnography (NPSG).

Thus far, a total of 43 patients have undergone an NPSG as a result of the answers to our screening questionnaire. Of these, 39 had an apnea/hypopnea index (AHI) greater than 5, indicating the presence of the obstructive sleep apnea hypopnea syndrome (OSAHS). The average AHI of those patients with OSAHS was in the moderate range at 27.5. Of those patients with OSAHS, 27 had an ESS score of 9 or greater, yielding a sensitivity of 0.69 for the ESS. The positive predictive value of the ESS was 0.87. There was no significant difference in age and sex between patients with an ESS greater than 9 and those with a score of 8 or less. The sensitivity and positive predictive value of the combination of a BMI greater than 25 and the presence of snoring was 0.94 and 0.92, respectively. There was a significant correlation between increasing BMI and AHI. No such relationship existed between ESS score and BMI. These preliminary data indicate that the sensitivity and positive predictive value of the ESS questionnaire in predicting the presence of SDB can be improved by evaluating patients with a BMI of 25 or greater who snore in addition to those with an ESS of 9 or greater.

***Clostridium perfringens* Sepsis in a Man Treated for Metastatic Prostate Cancer.**

J. Gibson. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Introduction: This is a case report of a 70-year-old man with metastatic prostate cancer treated with chemotherapy who was admitted to the medical intensive care unit with rectal bleeding and expired 4 days later of polymicrobial sepsis including widely disseminated *Clostridium perfringens*.

Methods: The patient's chart was reviewed and discussed with his primary oncologist. Members of the pathology department were consulted regarding the postmortem examination. A review of the literature was conducted using Medline. Search keywords were limited to "Clostridium perfringens," "sepsis," "docetaxel," "estramustine," and "colitis." References from the autopsy report where also reviewed.

Results: *Clostridium perfringens* sepsis is an unusual, often fatal infection associated with common medical conditions such as malignancy, treatment with chemotherapy, and bowel injury. Administration of taxane-based chemotherapy may cause an ischemic colitis allowing translocation of enteric bacteria including Clostridial species from gut to bloodstream. *C. perfringens* is usually sensitive to antibiotic therapy but bacteremia may be unrecognized by clinicians. Toxins produced by *C. perfringens* cause lysis of erythrocytes, platelets and neutrophils. This may prevent a reactive leukocytosis and blunt the inflammatory response. The high mortality rate of *C. perfringens* sepsis in part reflects the severity of the medical conditions associated with the infection.

Conclusion: Given the potential difficulty of recognizing Clostridial sepsis, even widely disseminated infections may go undiagnosed until postmortem examination. Empiric antibiotic coverage in settings predisposing to *C. perfringens* sepsis may reduce the infection's high mortality rate.

Increase in CD4 Lymphocyte Count Following Hepatitis C Viral Clearance in a Cohort of HIV/HCV Co-infected Individuals. A.J. Uriel[1], M. Abell-Rosen[1], A. Reichenberg[2], and D.T. Dieterich[1]. Departments of [1]Medicine and [2]Psychiatry, Mount Sinai Medical Center, New York, NY.

Conflicting evidence exists as to whether hepatitis C virus (HCV) has an adverse effect on immunological progression in HIV. We performed a retrospective analysis of the impact of clearance of HCV on CD4 lymphocyte count in 39 HIV/HCV patients treated with ribavirin (RBV) and interferon (IFN). Subjects were classified as sustained responders (SVR, n= 16) or non-responders (NR, n=23). Change in CD4+ counts 6 months after HCV treatment compared to baseline were analyzed for each group. The mean change in CD4 count was an increase of 61 × 10^6/l (±190) in the SVR group, and a decrease of 79 × 10^6/l (±158) in the NR group ($p=0.017$). This finding was independent of HIV suppression. Defining a significant change in CD4 count after treatment compared to baseline as either an increase or decrease of > 50 cells, 11/16 (68.7%) SVRs vs. 5/23 (21.7%) NRs had an increase, and 3/16 (18.7%) SVRs v 16/23 (69.6%) NRs had a decrease in CD4 count. (Chi squared test $p<0.018$). We conclude that co-infection with HCV negatively impacts CD4 recovery, even with effective HAART, and that achieving an SVR with IFN and RBV is associated with a rise in CD4 count of > 50 cells.

Chlamydia Trachomatis Infection in US Army Recruits. D. Haas[1], A.I. Choi[1], and S.G. Weber[2]. [1]Department of Medicine, Mount Sinai Hospital, New York, NY, and [2]Department of Medicine, University of Chicago School of Medicine, Chicago, IL.

Introduction: The prevalence rate of *Chlamydia trachomatis* infection in US Army recruits has been found to be as high as 9.2% using a screening urinary ligase chain reaction assay (ULCR). However, its prevalence in the US Naval population using different diagnostic assays has not been studied.

Methods: Chlamydia infection status by ULCR, endocervical ligase chain reaction (ELCR) and PACE-2 DNA probe was determined in 477 naval recruits from throughout the US between April 1999 to January 2000. Demographic data was obtained through a standard questionnaire. Univariate analysis was used to determine risk factors for infection. Kappa statistics were calculated to compare the three assays.

Results: Overall, sixty of the 477 subjects (12.6%) tested positive for infection with *C. trachomatis* by at least one of the three diagnostic assays. ELCR testing detected the greatest number of infections (n=54, 11.3%). In contrast, PACE-2 and ULCR identified a smaller fraction of infected subjects (n =25, 5.2% and n=30, 6.3%, respectively). Black recruits were nearly twice as likely to be infected (20.2% vs. 10.98%, $p=0.02$) with odds ratio by ELCR, 2.36 (95% CI 1.26–4.23). Kappa statistics revealed poor correlation between the results of the three assays.

Conclusion: The Navy should continue to screen the female recruit population for chlamydia, particularly those of black ethnicity. It should consider replacement of the PACE-2 assay with the ELCR assay or with dual screening using both the ELCR and ULCR assay for female recruits.

A Central Nervous System Metastasis of Thymic Carcinoma: A Case Report and Literature Review. C. Denlinger[1], B. Panzera[2], S.H. Gultekin[3], G. Forster[4], and A.P Chahinian[5]. Departments of [1]Medicine, [2]Medical Oncology, [3]Pathology and [4]Neurology, and [5]Ruttenberg Cancer Center, Mount Sinai Medical Center, New York, NY

Introduction: This is a case report and review of the literature regarding a patient with poorly differentiated thymic carcinoma and metastasis to the cauda equina.

Methods: The patient's records from 1999 through 2003 were reviewed. Medline was used to conduct a review of the literature. Search keywords limited to "thymic carcinoma," "malignant thymoma," "cauda equina metastasis," and "intradural metastasis." Relevant articles were then reviewed and cross-referenced.

Results: There are 19 reported cases of CNS metastasis from thymic carcinoma or malignant thymoma and less than 60 total cases of intradural extramedullary metastasis found in the literature. However, no other cases of thymic carcinoma with metastasis exclusively to the nerve roots of the cauda equina were identified. The most prominent presenting symptom of intradual extramedullary metastasis is lancinating radicular back pain that is worse with recumbency and awakens the patient at night. MRI is the most accurate tool for diagnosis. Treatment often involves surgical intervention with intradural exploration and tumor debulking, although debulking offers no survival benefit in patients with thymic carcinoma. Thymic carcinoma is extremely rare, with the incidence of metastasis being 15–155%. Metastasis to the CNS is extremely rare and portends a poor prognosis.

Conclusion: A comprehensive evaluation of a patient with back pain and a history of malignancy should include examination of the CSF for cytology and contrast-enhanced MRI to localize possible metastatic lesions.

Depressive Symptoms are Independently Predictive of Carotid Atherosclerotic Plaque. D.C. Haas[1], K.W. Davidson[1], D.J. Schwartz[1], N. Rieckmann[1], M.J. Roman[2], T.G. Pickering[1], W. Gerin[1], and J.E. Schwartz [3]. [1]Mount Sinai School of Medicine, and [2]Weill Medical College of Cornell University, New York, NY; and [3]SUNY - Stony Brook, Stony Brook, NY.

Background: Epidemiological studies indicate that depression is a risk factor for coronary heart disease (CHD), but the mechanisms linking depression to CHD remain unspecified. Experimental evidence suggests that depression may influence the expression of CHD by affecting atherosclerosis; however, few studies have examined depression and atherosclerosis in clinical populations. We examined this association by testing whether depressive symptoms predicted subclinical carotid plaque, a marker of coronary atherosclerosis.

Methods and Results: Healthy participants (n=219) enrolled in a prospective study of job stress and cardiovascular disease underwent baseline assessment of body mass index, 24-hour blood pressure, lipids, smoking, diabetes, and demographic variables. Depressive symptoms were measured with the Brief Symptom Inventory Depression subscale and partitioned into approximate quartiles. Carotid ultrasonography was performed to assess for atherosclerotic plaque after 10.5 years follow-up. Plaque prevalence increased across depression quartiles monotonically, from 40.9% to 61.5%. Adjusting for baseline covariates, participants in the two highest depression quartiles were more likely than those in the lowest quartile to have carotid plaque (odds ratio=2.21 [$p=0.04$] and 2.63 [$p=0.03$], respectively).

Conclusions: Depressive symptoms appear to be an independent risk factor for carotid atherosclerosis in this sample. Depression's epidemiological association with clinical CHD may stem from its influence on atherosclerosis.

The Use of Methadone for Chronic Pain: Palliation with Prudence. B.D. Russano and D. Fischberg. Mount Sinai Hospital, New York, NY.

Introduction: Much information and experience exist on the use of methadone for opioid addiction. Still, its use in the area of chronic pain should not be overlooked.

Methods: Inspired by the case of a hemiplegic patient with persistent neuropathic pain, a review of the literature was performed to ascertain what current trends exist for the use of methadone for chronic pain.

Results and Conclusions: Methadone is an effective and versatile analgesic that is unique in its advantageous pharmacokinetics, dynamics, and economics. However, methadone therapy is not without its risks. The drug must be vigilantly titrated to avoid dangerous side effects and potential drug interactions. When used correctly, its unique receptor properties provide a promising alternative or adjunctive medication in the quest for pain relief.

Incidence of Venous Thromboembolic Events among Low and Medium Risk Medical Inpatients in the Absence of Anticoagulant Thromboprophylaxis. M. Osofsky, J. Boxer, M. Skamagas, H. Patel, A. Federman, S. Goldberg and A. Dunn. Mount Sinai Hospital, New York, NY.

Introduction: Although hospitalized general medical patients often receive prophylaxis for venous thromboembolism (VTE) with heparin, there is little research examining the incidence of venous events in the absence of anticoagulant thromboprophylaxis in these patients.

Methods: We performed a retrospective review of inpatients from randomly selected admissions to the general medical wards of Mount Sinai Hospital between July 1, 2002 and December 31, 2002. Patients were excluded if they received subcutaneous heparin or were at high risk for VTE (prior VTE, active cancer, recent surgery). Thromboembolic events were assessed during the hospitalization. Subjects were divided *a priori* into subgroups with 0 VTE risk factors and with ≥ 1 VTE risk factors. VTE risk factors were CHF, CVA, obesity, age > 80, or immobility during hospital stay.

Results: Of 641 admissions identified, 595 (93%) were available for abstraction. In this preliminary analysis of 276 admissions, 177 met eligibility criteria. The mean age of patients was 58 ± 21 (range 20–97). 109 (62%) patients had 0 VTE risk factors and 68 (48%) patients had ≥ 1 risk factor. One thromboembolic event was noted (0.6%, 95% CI 0–3%). This patient had 2 risk factors for VTE. The VTE incidence for patients with 0 and ≥ 1 VTE risk factors were 0% and 1.5%, respectively.

Conclusions: The incidence of VTE in low/moderate risk hospitalized medical patients not receiving anticoagulant thromboprophylaxis is low. No events occurred in patients with 0 VTE risk factors. Further studies are needed to determine which medical inpatients are at sufficient risk to justify anticoagulant prophylaxis.

Variability of Lipid Screening and Control among Minority Populations in East Harlem. R. Levine Berger. Department of Medicine, Mount Sinai Hospital, New York, NY.

Background: Despite overwhelming evidence that lipid-lowering therapy significantly reduces mortality and cardiovascular events, current literature suggests that dyslipidemia remains underdiagnosed and undertreated. This is particularly true within minority communities and contributes to the significant disparity in health-related outcomes among minority populations.

Methods: Charts of African American, Hispanic, and White patients in a general adult medicine clinic who carried a diagnosis of hypertension were reviewed. Data from the previous two years was reviewed for the presence and values of a recent lipid profile, comorbidities, and treatment for hyperlipidemia. The low-density lipoprotein cholesterol (LDL-C) goals were determined as defined by National Cholesterol Education Program (NCEP) guidelines. The primary end point was the success rate of each ethnic group in meeting these goals.

Results: A total of 325 charts were reviewed. Of these, 88.6% had a lipid profile within the last two years. Overall, 54% had an LDL-C goal of <100 mg/dL, 31% had a goal of <130 mg/dL, and 14.7% had a goal of <160 mg/dL. African American and Hispanic patients were more likely to have an LDL-C goal of <100 mg/dL, 60.19% and 61.82% respectively, as compared to Whites for whom 41.07% reached goal (p=0.003). The overall achievement of LDL-C goals were 49.69% for those with a goal <100 mg/dL, 68% for <130 mg/dL, and 93.18% for <160 mg/dL. This did not vary significantly among the different ethnicities.

Conclusions: As compared to the literature, this population has a significantly higher rate of screening and achievement of LDL-C goals. Although the minority groups are more likely to have a lower LDL-C goal, there does not appear to be a significant difference in control rates.

Graft Vasculopathy: Comparison of Cyclosporine and Tacrolimus over 15+ years. D.A. Baran, S. Kaplan, S. Lubitz, I. Galin, S. Alvi, R. Correa, D M. Chan, D. Spielvogel, S.L. Lansman, and A.L. Gass. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: Transplant coronary artery vasculopathy is the major factor limiting long-term survival in post heart transplant patients. To assess if transplant vasculopathy is related to immunosuppressive regimen used, catheterization reports were retrospectively reviewed.

Methods: The catheterizations performed on the 246 patients who underwent heart transplant at Mount Sinai Medical Center between 1986 and 2003 were reviewed. These follow-up studies were performed at 4–6 weeks post-transplant and subsequently yearly. All catheterizations were reviewed by two observers blinded to immunosuppressive regimen.

The patients were divided into groups based on immunosuppressive regimen used. Group A consisted of patients on tacrolimus-based immunosuppression which included patients on tac monotherapy, tac +steroids and patients converted from cyclosporine to tacrolimus. Group B comprised patients on a cyclosporine-based regimen.

Results: 145 patients received tac-based therapy and 101 received cyclo-based therapy. There was a 33.6% incidence of transplant vasculopathy in the cyclosporine group vs. a 20% in the tac group (p=0.13). When divided into type of vasculopathy, 12% of patients in both groups had focal cad lesions while 20% of patients in cyclo group had diffuse vasculopathy vs. 8% in the tac group (p=0.001).

Focal and diffuse disease had a similar time of onset in both groups. Post-transplant survival was similar in both groups, although tac monotherapy had significantly longer post-transplant survival than cyclosporine group (p=0.004)

Conclusions: The 5-year incidence of transplant vasculopathy (both diffuse and focal) was 20–33%, but incidence of diffuse transplant vasculopathy was significantly lower in the tac monotherapy group.

Minimal immunosuppression with tac monotherapy is not associated with excess cad of either type.

Overall survival is longer in the tac monotherapy group vs. the cyclosporine group.

Using Structured Debate to Teach a Controversial Topic. I. Helenius[1], C. Goldstein[2], and D. Korenstein[1]. [1]Mount Sinai School of Medicine, New York, NY and [2]University of Calgary, Calgary, Alberta.
90

We designed an educational program using debate to (1) improve residents' ability to discuss controversial issues regarding mammography with patients, and (2) increase residents' confidence in clinical decision making regarding screening mammography.

Methods: We conducted a prospective cohort study on the effect of a teaching intervention for 2nd year medical residents between 1/03 and 9/03. The intervention consisted of a 3-hour structured debate on the merits of mammography for women in their 40s. Questionnaires were administered 2 weeks prior to and 3 months after each debate. Pre- and post-debate answers were compared using the Wilcoxon paired rank test.

Results: Thirty-three of 36 residents participated in the debates. 100% completed the pre- and post- questionnaires. 97% agreed that the debate was an effective teaching tool. Residents were divided on the question of whether they routinely recommend screening mammography to average risk women in their 40s both before and after. After the debate, 18 residents (54%) became more confident that their practices regarding screening mammography for women in their 40s were supported by the literature, and 5 (15%) became less confident (p=0.03). 16 (48%) residents reported an increase in comfort discussing mammography screening, 14 (42%) no change, and 3 (9%) a decrease (p=0.02). 25 (76%) became more likely to discuss screening mammography with their patients (p<0.001).

Conclusion: A structured debate on screening mammography for women in their 40's effectively improves residents' attitudes about discussing this controversial topic with their patients.

Research Day 2004 Queens Hospital Center

Case Report: Change in Mental Status in a Cardiac Patient. N. Gill and M. Anneneyie. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Though beta adreno-receptor blockers are known to produce CNS-related side effects, the reported incidence is quite low. We present a case of a cardiac patient, who came without any neurological deficits but went on to develop recurrent gross change in mental status with two different classes of beta blockers.

Case: A 69-year-old man from Guyana with diabetes mellitus and chronic renal insufficiency, hypertension, hyperlipidemia and exertion-related angina presented to the Emergency Department for two episodes of acute substernal chest pain at home, at rest, which responded to sublingual nitroglycerine. He denied any other symptoms.

On admission, his blood pressure was 210/100 mm Hg. He was fully alert and oriented with no significant physical findings except an uncomplicated umbilical hernia. His EKG showed LV strain pattern with poor R wave progression without any acute changes. He did not have any elevation of cardiac enzymes. His other lab results were within normal limits except for an increased serum creatinine which was his baseline since before admission.

He was admitted to the CCU for recurrent chest pain and uncontrolled blood pressure with the impression of unstable angina. While in the CCU, he received IV nitroglycerine drip for chest pain and IV Labelelol for hypertension along with heparin, aspirin, Lipitor, amlodipind and lansprozole at night. He did not receive any sedatives, antipsychotics or steroids. The next morning, he was still febrile and alert but appeared restless, confused and disoriented in place, person and time without any hallucinations or delusions. He thought that he was in Guyana. By the second day, his confusion had progressed but his neurological exam, routine blood work, including metabolic panel, CT of the head and CSF studies, did not show any evidence of sepsis or any metabolic abnormalities. At this point, his beta-blockers were discontinued. Next day, patient was calm and oriented to place, person and time. He answered questions appropriately.

Later in the day, when he was started on carvedilol (Coreg), he became agitated again. He started climbing out of bed, made sexual remarks to the nurses and cursed his family members. All of these symptoms resolved once again when carvedilol was stopped.

Discussion: Atenolol, metoprolol are relatively specific to cardiac beta-1 receptors whereas propranolol, carvedilol, are nonselective, though in higher doses all agents are nonselective. Propranolol, carvedilol, labetalol, metoprolol, pindolol, and timolol are lipophilic whereas Atenolol, bisoprolol, nadolol are water soluble with poor CNS penetration. Propranolol is the most widely studied agent of this class for CNS-related side effects. It is reported to cause severe toxic psychosis starting with mild perceptual errors progressing to severe confusional state. Patients with dementia have been reported to have developed vivid imagery and hallucinations and severe depression.

In all reported cases, even prolonged symptoms abated with the discontinuation or reduction of the beta-blocker drug and they recurred with rechallenge, as reported in our case. The mechanism of CNS side effects is due to its effect on centrally located beta adrenergic receptors, known to exist downstream from and at the terminal of "vigilance-enhancing" central nonadrenergic pathways. Cellular effects are due to membrane-stabilizing effect on central neurons. All beta blockers can give rise to CNS side effects, but the incidence varies depending upon the character of the drug, such as lipophilicity and hydrophilicity, the ratio of antagonist versus (partial) agonist properties, affinity to the receptor site, strength of membrane stabilizing activity and potency. It has also been proposed that CNS side effects may be related to depressed melatonin secretion.

Conclusion: It is suggested that in all cases of altered mental status with no other evident cause, the use of beta-blocker drugs must be reviewed and should be discontinued if suspected to be the cause. If the symptoms resolve with discontinuation of beta blockers and recur with resumption, then the most likely cause is the beta blocker. Hence, it is a diagnosis of exclusion. If continuation is necessary, a weakly lipophilic agent such as atenolol in low doses, should be tried.

Systemic Lupus Erythematosus during the Treatment with Interferon-alfa for Chronic Myeloid Leukemia. G. Gupta and A. Opran. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: With the rapid developments in the field of biotechnology, there have been several important developments involving immunotherapy to treat various malignancies and viral hepatitis. Alfa interferon (INF-a) is one of the most significant of these developments. The treatment with INF-a has been linked with the development of autoimmune disorders. SLE induced by INF-a therapy is not usually associated with significant CNS or renal involvement.

We report a patient who was treated with INF-a for CML for approximately 20 months, and while on therapy, developed SLE with renal and CNS manifestations.

Case Report: A 36-year-old African American woman with hypothyroidism was diagnosed with chronic myeloid leukemia (80.8x10e3 with no blasts) in 2001. She was started on treatment with INF-a 2b (7 million units SQ daily). She underwent complete remission by Karyotyping and Fluorescence In Situ Hybridization (FISH) assays performed on bone marrow biopsy specimen approximately 1½ years later. She was continued on INF-a for maintaining remission. Patient remained clinically stable until 1 year later, when she experienced 3 episodes of transient dysarthria, word-finding difficulty and non-focal weakness associated with frequent headaches. About the same time she developed progressively increasing patchy alopecia and maculopapular rashes on the face and neck. Due to these neurological symptoms and worsening dermatological status, INF-a was discontinued and the patient was started on imatinib mesylate (Gleevec). Despite this therapeutic intervention patient continued to experience repeated episodes of transient dysarthria and lower extremity weakness with worsening of skin rash, and she was admitted to our hospital for further workup. She denied any history of arthralgia, joint inflammation, miscarriage, dry mouth, dry eyes, pleuretic chest pain, shortness of breath, or lower extremities swelling. Physical examination showed maculopapular rashes on the face and neck. Neurological examination was non-focal. At this time work-up for possible autoimmune disease was ordered. Immunofluorescence assay for serum double stranded DNA antibody titer was elevated at 1:160. Antinuclear antibody (ANA) titer was also elevated at the level of 1:1280 with a homogenous pattern. This was associated with drop in Complement 3 and Complement 4 to the level of <39 and <10 respectively. Anti-sm-RNP was low positive, anti-Sm antibody was positive at 1:20 with negative anti-Ro, anti-La antibody by immunofluorescence assay. Peripheral blood smear was positive for leukocytopenia, thrombocytopenia and anemia (hemolytic). Patient's urine analysis was significant for proteinuria of 0.9 gm/24 hr and hematuria. Her BUN/creatinine increased from baseline of 8/0.8 mg/dL to 21/1.7 mg/dL with persistent hematuria. Lumbar puncture showed increased proteins at the level of 133 mg/dL. EEG was abnormal, which was suggestive of diffuse cerebral dysfunction. Patient had 6 out of 11 criteria for diagnosis of SLE. Renal biopsy for persistent hematuria and proteinuria was highly characteristic of focal lupus glomerulonephritis with mild to moderate activity, with no chronic changes. Patient was treated with intravenous methylprednisolone succinate, which was changed to oral prednisone 1 mg/kg/day and later on tapered to 5 mg po qd. Over the course of about 7 months patient's symptoms improved tremendously. She denies having any neurological and dermatological symptoms. At this time her anti-DNA antibodies are negative, with decrease in ANA titre and increase in complement levels.

Conclusion: We report a rare case of SLE developing during the course of INF-a therapy for CML with early significant renal and CNS involvement. Patients treated with INF should be closely monitored for autoimmune symptoms, so that early diagnosis and therapeutic intervention may potentially be life saving.

Giant Parathyroid Adenoma with Persistent Hypercalcemia. P. Kim, M. Nukala, D. Reich, and I. Sachmechi. Department of Medicine, Mount Sinai School of Medicine at the Queens Hospital Center, Jamaica, NY.

Introduction: In general, a parathyroid adenoma weighs between 300 mg and several grams, and its size varies from less than 1 cm to more than 3 cm. We report a rare case of a giant parathyroid adenoma weighing 12 grams, which caused the patient to have clinical confusion due to an atypical presentation.

Case Report: A 75-year-old man without significant medical history was admitted to the hospital with confusion and a serum calcium level of 11.8 mg/dL (8.5–10.5 mg/dL) with serum albumin of 3 grams/dL. The work-up revealed primary hyperparathyroidism with a markedly increased intact PTH serum level of 1423.5 pg/mL (10–65 pg/dL). Interestingly, the imaging studies, including ultrasound, CT scan, and Sestimibi scan, suggested a large neck mass arising from the thyroid, measuring 3.6 × 3.5 × 2.9 cm instead of a typical parathyroid lesion. Given the clinical possibility of parathyroid carcinoma, along with symptomatic hypercalcemia and renal failure with BUN/creatinine of 32/3.3 mg/dL, the patient underwent resection of the neck mass, which was confirmed to be a giant parathyroid adenoma weighing 12 grams. The post-op course was uneventful and serum calcium normalized.

Discussion: A giant parathyroid adenoma could cause clinical confusion among the medical staff due to an atypical clinical presentation. Due to its strikingly large size, a giant parathyroid adenoma may appear to be a thyroid lesion in imaging studies. Also, the possibility of parathyroid carcinoma has to be entertained, because parathyroid carcinoma can also present with iPTH levels 3 to 10 times above the upper limit of normal and weigh as much as a giant parathyroid adenoma.

Conclusion: A giant parathyroid adenoma is a rare cause of primary hyperparathyroidism, which can cause clinical confusion due to the atypical presentation. The largest parathyroid adenoma reported was 39.5 grams. This case of a giant parathyroid adenoma is the second largest reported case in the literature.

Recurrent Cardio-pulmonary Arrest. J. Kandala and R.A. López. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

JW is a 78-year-old female resident of a nursing home who presented with sudden shortness of breath, productive cough with difficulty in "bringing up the phlegm" and hoarseness. While talking to her family, she suddenly started choking and became unresponsive for approximately 3 minutes. Nursing Home personnel described this episode as air hunger or choking; the patient was hypertensive, tachycardic, and tachypneic upon evaluation by the emergency medical service (EMS).

The patient has multiple medical problems including diabetes mellitus, peripheral vascular disease, ESRD requiring hemodialysis, clinically suspected OSAS and a childhood history of asthma. Her daily activities include bed to chair activities. She had undergone endotracheal intubation five times for operative procedures as well as for previous cardio-respiratory arrests precipitated by respiratory distress, most recently one month earlier.

Upon evaluation in the Emergency Department the patient refused endotracheal intubation, and treatment for asthma exacerbation was initiated; an ICU consult was requested.

Physical examination revealed an obese woman in obvious distress, speaking in 2-4 word phrases with a hoarse voice and stridor. She had macroglossia and a fatty, short neck with no thyromegaly, no JVD or lymphadenopathy. Her lungs revealed decreased air entry bilaterally with transmitted wheezing and no rhonchi. Neurological examination was normal. Laboratory studies revealed leukocytosis and anemia, a chemistry panel consistent with ESRD. Blood gas analysis revealed respiratory acidosis. Her chest X-ray revealed cardiomegaly and an EKG was unremarkable.

While in ICU, intermittent NPPV in addition to therapy initiated in the ED provided partial improvement. Myocardial infarction and pulmonary embolism were ruled out. Spirometry demonstrated suboptimal efforts but no evidence of upper airway obstruction. A fiber-optic evaluation of the upper airway by ENT and CT of the neck were normal. Bronchoscopy also revealed a normal upper airway, but edema and thick mucus were present in the subglottic area. The vocal cords were normal; erythema was also present below the vocal cords with abundant mucus. Approximately 4 cm below the vocal cords a 1 cm long concentric stenotic lesion was visualized. The bronchoscope (external diameter 5 mm) passed the lesion, but not without causing respiratory distress to the patient. The distal trachea was normal.

The patient was transferred to a tertiary care center where she underwent tracheal resection of the lesion with an end-to-end anastomosis. She tolerated the procedure well, quickly recovered and was discharged back to her nursing home.

Discussion: Progressive dyspnea and wheezing unresponsive to bronchodilators, coupled with a history of recent or repeated episodes of respiratory failure, are important indicators of tracheal stenosis. Symptoms at rest are uncommon and only appear when the tracheal diameter reaches a critical threshold. Patients frequently defer seeking medical attention, attributing their symptoms to other causes. Tracheal stenosis after intubation is often misdiagnosed as asthma, as in this case. Recurrent cardiopulmonary arrest has not been reported as an indicator of tracheal stenosis. Our patient highlights the need for prompt diagnostic testing in the appropriate clinical scenario. Bronchoscopy in this setting is preferably performed in an intubated patient; this case proved that albeit at greater risk, it remains the diagnostic gold standard, and tracheal stenosis should be considered in patients presenting with repeated cardiopulmonary arrest of unknown etiology.

Tuberculosis of the Breast Masquerading as Inflammatory Breast Cancer. U.A. Ireh and B. Morel. Department of Surgery, Queens Hospital Center, Jamaica, NY.

Introduction: Tuberculosis of the breast is rare. We report the case of a 40-year-old Nigerian woman immigrant with a positive family history of breast cancer, who presented with breast, axillary masses, and skin changes. She underwent an excisional biopsy after mammography. Pathological diagnosis was consistent with tuberculosis. The patient was referred for medical management and was subsequently started on appropriate anti-mycobacterial therapy. The suspicion for tuberculosis should be high, given a compatible history of immune-depression, foreign travel or close contact with a patient with active disease. A surgeon should, in the right historical setting, have an early suspicion of extrapulmonary TB when confronted with an axillary or breast mass with dermal-lymphatic invasion.

Objective: Against the background of a compatible history, inflammatory breast cancer is typically diagnosed from physical examination by a characteristic dermal-lymphatic invasion presenting as *peau d'orange*. Extrapulmonary tuberculosis of the breast and the axilla can masquerade as inflammatory breast cancer by a similar dermal-lymphatic invasion. The case of the 40-year-old female immigrant with a positive family history of breast cancer is presented and reviewed to show that tuberculosis should be high on the differential diagnosis of any breast and axillary mass. The suspicion for tuberculosis should be high, given a compatible history of immuno-depression, foreign travel or close contact with a patient with active disease.

Study Design: Clinical case presentation and review of the literature.

Results: TB of the breast is rare. However, given an appropriate history, extra pulmonary TB of the breast could present with dermal-lymphatic invasion and *peau d'orange* that are characteristic of inflammatory breast cancer. While Tb of the breast is more common in developing regions, such as the Indian subcontinent, and sub-Saharan Africa, foreign travel and human immunodeficiency syndrome increase the risk of breast TB in the United States. The clinicians should be aware of this increased risk.

Conclusion: In this age of high immigration, immunodeficiency diseases, and likelihood of a close contact with a TB-infected patient, the physician should have an early suspicion of extrapulmonary TB when confronted with an axillary mass, and breast lesion with dermal-lymphatic invasion. Early diagnosis of TB not only saves the patient unnecessary therapy, but also protects health care workers from unnecessary exposure to the disease.

Spontaneous Remission of B-Cell Non-Hodgkin's Lymphoma Following Withdrawal of Methotrexate in a Patient with Rheumatoid Arthritis. D. Nagarajan, S. Adusumilli, and I.J. Tan. Department of Medicine, Mount Sinai School of Medicine at Queens Hospital Center, Jamaica, NY.

Introduction: Rheumatoid arthritis (RA) is an autoimmune disorder with an increased risk of lymphoproliferative disorders. The association with malignancy has been described in both RA alone, and in RA in combination with disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate. Herein we describe a 51-year-old female with RA who developed lymphoma after treatment with methotrexate. The lymphoma underwent remission following withdrawal of methotrexate.

Case Presentation: A 51-year-old woman with of hypertension and sero-positive RA since 1991 presented to Rheumatology Clinic in the summer of 2002, complaining of a 3-week history of decreased appetite, night sweats, fatigue associated with tender swelling under the jaw for 10 days. She denied any fever. She was initially treated with hydroxychloroquine, prednisone, and nabumetone for RA. Her symptoms of RA remained active, so oral methotrexate 7.5 mg weekly was added in 1995. Due to active synovitis, oral methotrexate was increased to 12.5 mg weekly in March 2000. Leflunomide was added in the fall of 2001. The patient's arthritis symptoms were well-controlled with methotrexate 12.5 mg weekly, leflunomide 20 mg daily, and celecoxib 200 mg twice daily as needed since 2001.

On physical examination, her temperature was 98.4°F, blood pressure was 126/64 mm Hg, heart rate was 60 beats per minute, and respiratory rate was 12 per minute. There were tender lymph nodes involving bilateral submandibular, cervical, axillary, left supraclavicular and bilateral inguinal areas, the largest approximately 2.5 cm × 2.5 cm in size. There were no skin lesions, no active synovitis, and examination of the heart, lungs, abdomen, and nervous system was unremarkable.

The patient was admitted for lymph node biopsy with a presumptive diagnosis of tuberculosis (TB) versus lymphoma (primary vs. methotrexate-induced). Methotrexate was discontinued. Laboratory tests done at the time showed: white blood cell count 7,400/mm^3 (4,500 – 11,000/mm^3), hemoglobin 12.3 g/dL (11.5 – 13.1 g/dL), hematocrit 38.2% (37 – 47%), erythrocyte sedimentation rate of 60 mm/hr (0 – 20 mm/hr). A test for Epstein Barr virus later was positive for IgG. Pathology report of the cervical lymph node biopsy revealed B-cell follicular non-Hodgkin's lymphoma.

The patient was referred to Oncology Clinic for staging and further management. CT scans of the thorax, abdomen, and pelvis revealed lymphadenopathy above and below the diaphragm, Gallium scans demonstrated increased uptake in the patient's hilar regions and the mediastinum. Bone marrow biopsy was positive for lymphoma cells. A diagnosis of grade II, stage IV B-cell follicular non-Hodgkin's lymphoma (NHL) was made. However, chemotherapy could not be started, as the blood count showed eosinophilia (16%), and stool studies confirmed the presence of strongyloides. The patient was treated with albendazole. Eight weeks following the discontinuation of oral methotrexate, and without the initiation of any chemotherapy, the lymph nodes were no longer palpable. After 2 months of watchful waiting, the patient's constitutional symptoms resolved spontaneously. Repeat CT scans were normal with no lymphadenopathy noted. To date, the patient remains clinically stable with no signs or symptoms of lymphoma, and her RA is being treated with hydroxychloroquine, celecoxib and sulfasalazine.

Discussion: Studies have shown that the ability of T-cells to control Epstein-Barr virus (EBV) is reduced in RA. This may predispose RA patients when treated with immunomodulating agents, such as methotrexate, to lymphoproliferative disorders. However, controversy remains as to the etiology of neoplasia in RA.

Conclusion: Methotrexate-induced NHL may occur in the setting of RA. Awareness of this potential complication of methotrexate could avoid potentially unnecessary, and even harmful treatment with chemotherapy. Withdrawal of the drug should be the first line of treatment before chemotherapy is considered.

Adult Onset Still's Disease (a Classic Presentation). S. Nalmas, S. Qureshi, and I. Tan. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Adult onset Still's disease is a rare inflammatory disease characterized by high spiking fever, evanescent salmon-colored rash, arthritis, hepatosplenomegaly and lymphadenopathy. In 1896, George Frederick Still, a British pediatrician, first described the childhood form of the disease (systematic form of juvenile rheumatoid arthritis), and in 1971 Bywaters reported the adult form of the disease.

This article describes the case of a 44-year-old Hispanic man who presented with recurrent fever, rash, arthralgia and weakness, with subsequent resolution of symptoms with treatment (steroids).

Laboratory studies revealed leucocytosis (12 – 20.5 k/mcL), elevated ESR (125 mm/hr), anemia of chronic disease (hemoglobin 10.6 – 13.2 g/dL, iron 1 mcg/dL, TIBC 182 mcg/dL, Ferritin 10,745 ng/mL) and hypoalbuminemia (albumin 2.1 g/dL). Radiographs of wrists and knees revealed mild osteoarthritic changes, while elbow and chest radiographs were normal. CT of the abdomen was consistent with mild splenomegaly and thoracic CT revealed bilateral axillary lymphadenopathy (and multiple nodes in the aortopulmonary window and right hilar region), lymph node and bone marrow biopsy ruled out for sarcoidosis and lymphoma, and the diagnosis of AOSD was made. The patient was treated with prednisone 20 mg once a day, Celebrex 200 mg twice a day, Plaquenil 200 mg twice a day with resolution of fever and rash in three days. He was then discharged home. The patient was followed in rheumatology clinic 3 times after discharge, with recurrence of rash twice for a transient period (1 day) followed by complete resolution of symptoms with tapering dose of prednisone.

AOSD has an incidence of 0.16 per 100,000 per year, with equal sex distribution and a bimodal age distribution with peak incidence between 15 – 25 and 36 – 46 years of age. This disease is not familial but is associated with HLA B17, B18, B35 and DR2.

The exact etiology of AOSD is unknown. However, infectious agents such as rubella, echovirus 7, mumps, Epstein Barr virus, cytomegalovirus, parainfluenza and parvovirus and bacterial infections such as yersinia, enterocolitica and mycoplasma pneumonia have been suggested as etiologic agents.

Affected patients may have increased blood levels of CRP, leukocytosis and anemia. Ferritin and IL-18 can be sensitive indicators of disease activity, IL-18 in particular being a reliable indicator of severe liver dysfunction.

Treatment of AOSD consists of NSAIDS, corticosteroids and immunomodulating drugs, depending upon severity of disease and internal organ involvement. NSAIDS, including aspirin, are the first line of treatment requiring high therapeutic levels of salicylates (15 – 25 mg/dL). A good initial response predicts a good long-term prognosis. Patients with debilitating joint symptoms, very high fever or internal organ involvement require corticosteroid treatment, oral or IV.

Methotrexate can be used as a steroid sparing agent for controlling systematic manifestations of the disease.

Preliminary studies using etanercept (anti-TNF alpha) have been promising. The course of the disease can be self-limited, intermittent or chronic, with functional status varying from good to chronically debilitating.

The prognosis of the disease is poor if it involves many joints or proximal or root joints, or if patient requires systemic steroids for more than 2 years. On the other hand, the presence of HLA-B35 is a good prognostic factor.

Henoch-Schonlein Purpura in a 43-Year-Old Male. A. Nasir, S. Alwani, S. John, V. Jonnalagadda, and I.J. Tan. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Henoch-Schonlein purpura is a rare systemic vasculitis, more commonly seen in children than in adults. We present a classic case of Henoch-Schonlein purpura in a 43-year-old adult male.

Case Presentation: A 43-year-old-male originally from India presented, complaining of non-pruritic, non-painful purpuric rashes on the lower extremities extending to the trunk for 10 days. The rash was associated with decreased appetite and weight loss of 15 pounds, generalized abdominal pain and loose bowel movements for 4 – 5 days. He had experienced cold symptoms 15 days prior to skin eruptions, and arthritis of the fingers, ankle and foot, for which he used ibuprofen.

On physical examination, blood pressure was 115/90 mm Hg, heart rate was 75, temperature was 99.2°F, and the respiratory rate was 20 per minute. He had non-tender, non-blanching, palpable, erythematous-purpuric rashes scattered over both lower extremities and trunk. Hepatomegaly was noted and the right lower quadrant of the abdomen was tender without guarding or rebound.

Blood tests revealed white blood cells of 9.5 k/mcL (4.5 – 11 k/mcL), hemoglobin of 14.7 g/dL (12 – 16 g/dL), hematocrit 44.1% (37 – 47%); platelet count was 261 k/mcL (130-400 k/mcL), BUN/creatinine was 14/1.7 (8 – 22/0.4 – 1.6 mg/dL). Urine analysis showed 0 – 2 red blood cells, and 24-hour urine protein was 3.4 g (0.3 – 1.5 g) and creatinine 1.7 (1.0 – 2.0 g). C-reactive protein 2.15 (0 –0.8 mg/dl), rheumatoid factor <20, anti-glomerular basement membrane antibodies were negative. Serum protein electrophoresis showed increased IgA at 590 mg/dL (59 – 485 mg/dL); complements C3 and C4 were normal. Both anti-proteinase antibodies and myeloperoxidase antibodies for ANCA were negative.

Abdominal CT scan showed thickened terminal ileum. The patient was admitted to surgery, where Tequin and Flagyl were given for ileitis and diarrhea. Infectious Diseases consult believed the rash was due to leukocytoclastic vasculitis. Colonoscopy done on hospital day #4 was significant for ileitis and discrete small rectal ulcers. The rash improved spontaneously by day 6, and he was discharged home.

Two days after hospital discharge, he was readmitted for arthralgias and worsening rash extending to the genitalia. He denied abdominal pain, diarrhea and fever. Rheumatology consult recommended skin biopsy for vasculitis. Dermatology suggested prednisone at 60 mg daily and then taper. Skin biopsy done confirmed leucocytoclastic vasculitis. Immunofluorescence was not performed. By day 4, the rash improved and the patient was sent home.

Five months later, the patient returned to Rheumatology clinic with reappearance of rashes and joint pain. Proteinuria (3+), microhematuria (red blood cells 50 – 100) occurred, along with uncontrolled hypertension and worsening renal function (BUN/creatinine 23/1.6). A renal biopsy done 8½ months later revealed IgA deposits in the capillary walls consistent with Henoch-Schonlein purpura.

Conclusion: Henoch-Schonlein purpura in adults tends to have more severe renal involvement. This is a case of HSP with the classic tetrad of rash, arthalgias, abdominal pain and renal disease manifesting over a period of 5 months.

Varicella Presenting as Cerebellar Ataxia. D. Noel, D. Nagarajan, and I.J. Tan. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Varicella, or chickenpox, is caused by varicella zoster virus (VZV). Herpes zoster is a separate clinical disease entity that follows reactivation of VZV after primary infection, during which the virus establishes latency in the dorsal ganglion cells. Varicella is predominantly a childhood illness with peak incidence in children aged 1 – 6 years, and more than 90% of cases occur in children under 10 years. When primary varicella infection occurs in adults, neonates or immunocompromised individuals, it generally causes a more severe illness associated with high morbidity and even mortality. We report an 81-year-old man who presented with cerebellar ataxia followed by painless skin eruptions typical of chickenpox.

Case Report: An 81-year-old male with medical history significant for type 2 diabetes mellitus and COPD presented to the Emergency Department with a 2-day history of left ear tinnitus, unsteady gait and giddiness, which he further described as his head 'swinging.' He had been using Atrovent and albuterol MDI, aspirin 81 mg, and glyburide 2.5 mg, with no recent changes to this regimen. His diabetes was well controlled, with glycosylated hemoglobin levels ranging from 6.8 – 7.6 %. He denied weakness, headaches, diplopia or slurred speech but thought he had a low-grade fever. A temperature of 100.6°F was noted in the ED.

Physical examination was notable for mild dysmetria on the left, left dysdiadokinesia, a wide-based hesitant gait and mild splenomegaly. There was no nystagmus or other focal neurologic deficit. CT scan of the brain showed microvascular ischemic changes but no acute pathology. Subsequent MRI/MRA showed diffuse white matter disease, likely microvascular disease, with normal posterior fossa and circle of Willis.

Thirty-six hours following admission, the patient developed a diffuse maculopapular rash with sequential progression to vesicles, pustules, and crust formation. There was no dermatomal pain or distribution of the rash. Further history revealed no prior history of varicella and a recent exposure to an infected daughter. The patient was treated with acyclovir 800 mg five times daily and was asymptomatic at discharge, with complete resolution of his presenting symptoms. Serology was positive for varicella IgM antibodies.

Discussion: This is a case of primary varicella infection in an elderly patient with cerebellar ataxia being the first manifestation. It is also likely that the patient had viral inflammation of cranial nerve VIII by VZV as suggested by the ENT consult. The history of exposure, characteristic maculopapulovesicular rash at different stages and the high varicella IgM titres suggest primary varicella, which is rare in the elderly and can cause a severe illness with increased morbidity when it occurs. The patient was hospitalized early, received adequate supportive care in addition to acyclovir, and recovered completely with no complications.

Conclusion: We report the first case of primary varicella infection in an elderly patient with cerebellar involvement. This cannot be herpes zoster, as the distribution of vesicles was not dermatomal.

Retroperitoneal Fibrosis Causing Bilateral Ureteric Obstruction and Obstructive Nephropathy in a 63-Year-Old Presenting with Syncope. D. Noel, D. Nagarajan, and I.J. Tan. Department of Medicine, Mount Sinai School of Medicine, Queens Hospital Center, Jamaica, NY.

Introduction: Retroperitoneal fibrosis (RPF) is a rare inflammatory disease characterized by extensive fibrotic tissue in the retroperitoneum. Most cases of RPF are idiopathic, but association with drugs (methysergide, carboplatin) malignancy, infection, connective tissue disorders, systemic vasculitis and aortic aneurysm has been described. We report a patient presenting with syncope, who was found to be uremic with obstructive renal failure secondary to idiopathic retroperitoneal fibrosis.

Case Report: A 63-year-old female with no significant medical history and not on medications, presented to Emergency Department following syncopal episode lasting two minutes and occurring as she stood up from a chair. She complained of a two-month history of malaise, back pain, poor appetite, a 20-lb weight loss; and intermittent nausea and vomiting for two weeks. She was dehydrated, tachycardic with elevated blood pressure and orthostatic on presentation. Physical examination was otherwise unremarkable.

Initial laboratory investigations were notable for an elevated ESR of 92 mm/h, BUN of 60 mg/dL, creatinine of 7.5 mg/dL, hyperkalemia and mild hyperchloremic metabolic acidosis. Renal sonogram showed small kidneys with bilateral hydronephrosis, and subsequent CT scan showed a soft tissue density beginning below the superior mesenteric artery encasing the aorta, proximal left and right ureters, inferior vena cava and proximal iliac arteries. Renal function scan with lasix revealed poor function of the left kidney and a UPJ obstruction in the right kidney. Bilateral percutaneous nephrostomy tubes were placed, with conversion to bilateral internal urethral stents three days later. Percutaneous CT guided core needle biopsy of para-aortic mass was done and result showed fibrous tissue, partly hyalinized with scattered chronic inflammatory cells. Work-up for malignancy initiated prior to pathology was negative.

In addition to relief of urethral obstruction, prednisone therapy was also initiated. Renal function normalized prior to discharge eleven days later. Three months later, urethral stents were removed, renal function remained stable, ESR normalized with complete resolution of constitutional symptoms, and prednisone was tapered. One year after removal of urethral stents, normal renal function was maintained. There was no recurrence of systemic symptoms, and no radiographic evidence of hydronephrosis, and the patient is normotensive with normal ESR.

Discussion: This patient presented with syncope that was found to be a manifestation of an underlying complex and poorly understood pathologic process. Uremic symptoms of nausea and vomiting resulted in volume depletion causing orthostatic hypotension and syncope. The patient had acute or chronic renal failure on presentation. Early recognition and treatment of an obstructive nephropathy, as well as the underlying pathologic process, was vital to her recovery. Previously, surgical uterolysis to free the ureters with omental wrapping to prevent re-obstruction was the treatment of choice for RPF. Review of recent literature, however, showed good results with periodic urethral stenting in combination with prednisone. Success was also achieved with other immunosuppressive drugs, such as azathioprine and cyclophosphamide; and tamoxifen. We were able to achieve remission in this patient by early decompression and bilateral urethral stenting for three months, in addition to prednisone therapy.

Rare Presentation of Multiple Autoimmune Disorders in Graves' Disease. G. Parikh, A. Sapadin, D. Reich, and I. Sachmechi. Department of Medicine, Mount Sinai School of Medicine at the Queens Hospital Center, Jamaica, NY.

A 32-year-old African American woman with a history of Graves' disease, myasthenia gravis, thymectomy performed 12 years ago and pancytopenia was admitted following a suicide attempt. Physical exam was remarkable for a pulse rate of 140 bpm, diffuse goiter with bruit, exophthalmos, and perioral and intraoral vesicular blisters. Treatment with propranolol and propylthiouracil (PTU) was initiated. Due to worsening leukopenia and obstructive symptoms manifested by dysphagia, total thyroidectomy was performed. Laboratory evaluation was significant for pancytopenia, with white cell count of $3700/mm^3$ (normal: $4.5-11\times1000$), platelets, $72{,}000/mm^3$ ($130-400\times1000$), hematocrit 31.2 (37–47%), thyroid stimulating hormone (TSH) level of <0.06 mIU/mL (0.2–6), thyroxin (T4) >24 mcg/dL (4.5–12), triiodothyronine (T3) 516 ng/dL (45–150), free T4 >6 ng/dL (0.71–1.85). Erythrocyte sedimentation rate was 40, ribonucleoprotein negative, Smith antibody negative, Sjogrens/ Ro antibody positive, antihistone antibody positive, complements C3-58 mg/dL (104–187), C4-12 mg/dL (21–87). Skin biopsy with direct and indirect immunofluorescence showed in vivo ANA and anti-type VII collagen, consistent with bullous lupus. After treatment with isotretinoin and dapsone orally, new blister formation ceased. After surgery the patient eventually became hypothyroid, requiring replacement therapy with Synthroid. Her hospital course required therapy for myasthenia gravis with pyridostigmine.

Antithyroid drugs like PTU and methimazole have been shown to induce skin eruptions similar to lupus. These cases are usually characterized by a positive antihistone antibody, but other lupus related serologic tests are negative. Our case is unique, as skin manifestations were not drug induced. It was unclear if pancytopenia was true autoimmune pancytopenia, secondary to Graves' disease or secondary to lupus. This is a unique case of Graves' disease associated with myasthenia gravis and bullous lupus.

Pseudo-Cushing's Disease Due to Domperidone. I. Sachmechi and G. Mansouri. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Domperidone is a peripheral dopamine antagonist. It increases esophageal peristalsis and increases lower esophageal sphincter pressure, gastric motility and peristalsis, and enhances gastroduodenal coordination. Therefore, the end result is facilitating gastric emptying and decreasing small bowel transit time.

Case Report: We present a patient with an incidental left adrenal mass in whom domperidone caused false elevation of urinary cortisol. The patient was a 64-year-old woman who presented with a chief complaint of abdominal discomfort, constipation, and bloating. The patient had no significant medical history except for a history of fatigue. She was seen by a gastroenterologist and diagnosed to have GI motility disorder. She was treated with domperidone that was provided to her by her physician in Canada. As part of her work-up, she received an abdominal CT scan, which showed a 1.5 cm mass in the left adrenal gland. She denied any history of weight gain, easy to bruise, polyuria, polydipsia and hirsutism.

On physical examination, her BP was 110/70 mm Hg, but she had no stigmata of Cushing syndrome. Further examination and testing revealed: WBC of 7.5 k/mcL with normal differential; a fasting blood glucose of 84 mg/dl; cortisol level after 1 mg overnight dexamethasone <4.6 mcg/dL; a 24-hr urine cortisol 247 mcg and 168 mcg at different times; an A.M. cortisol 12.9 mcg/dL, and P.M. cortisol 5.9 mcg/dL; and an ACTH of 24 mcg/dL; normal bone density.

When off domperidone: a 24-hr urine cortisol 89 mcg; 24-hr urine cortisol after low dexamethasone suppression test <5 mcg.

Discussion: In this case, after stopping domperidone, the 24-hr urine cortisol decreased significantly and the post-low-dose dexamethasone suppression test was less than 5 mcg, which basically ruled out Cushing syndrome. Some studies show that domperidone does not increase the serum ACTH or cortisol level, so the mechanism of increased urine cortisol in this case is not the elevation of serum cortisol. Thus, the domperidone falsely increased the level of 24-hr urine cortisol.

Conclusion: From this case, it is suggested that domperidone may artificially increase the level of urine cortisol measured by tandem mass spectrophotometry. However, the explanation for this observation is not yet clear. If the 24-hr urine cortisol level is high in a patient who is on domperidone, it is critical to distinguish pseudo-Cushing's syndrome—which is caused by the domperidone—from true Cushing's syndrome (by withholding domperidone and repeating the urine cortisol) to prevent unnecessary and potentially harmful treatment to the patient.

HTLV-1 Infection Presenting as Granulomatous PCP and Hypercalcemia with Normal 1,25 $(OH)_2D$ and PTHrp Levels. S. Shahnaz, D. Arevalo-Valencia, S. Kucinska, D. Reich, J. Tulczynska, and J Fleischman. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Since the initial description of human T cell lymphotropic virus (HTLV-1), clusters of this infection have been detected in Japan, the Caribbean, the southwestern United States, sub-Saharan Africa, Iran and Europe. Unlike human immunodeficiency virus (HIV) infection, most patients infected with HTLV-1 remain asymptomatic throughout their lifetime.

We report the case of a previously healthy 39-year-old Caribbean male with HTLV-1 infection presenting as hypercalcemia and granulomatous PCP. Interestingly, the hypercalcemia presented with normal PTHrP and 1,25 dihydroxyvitamin D ($1{,}25(OH)_2D$) levels, and the presence of *Pneumocystis carinii* in the granulomas was diagnosed with transbronchial biopsy taken during bronchoscopy. This is believed to be the first description of this type of reaction to *P. carinii* in an HTLV-1 infected/non-adult T-cell leukemia lymphoma patient.

Hypersensitivity Vasculitis. H.M. Duncan[1] and I.J. Tan[2], [1]Senior Medical Student, Ross University School of Medicine, Dominica, and [2]Department of Medicine, Mount Sinai School of Medicine at Queens Hospital Center, Jamaica, NY.

Introduction: Hypersensitivity vasculitis may be classified into 2 forms depending on whether or not there is internal organ involvement. Patients who have only skin purpura are said to have cutaneous leukocytoclastic vasculitis. Systemic involvement may be due to microscopic polyangiitis. Drugs and infections are common causes of hypersensitivity vasculitis. We describe a 21-year-old patient who presented with a palpable, purpuric rash on her lower extremities.

Case Presentation: The patient is a 21-year-old woman on no medications with a chief complaint of rash on her lower extremities. She first noticed the rash in early 2004. She stated that the rash was on her lower extremities and lasted for 4 days and resolved on its own. The same type of rash recurred about 15 days later, this time affecting a larger area of her lower extremities. She went to the ER, and was given an appointment for the dermatology clinic. There she was diagnosed with leucocytoclastic vasculitis (no biopsy was done) by the dermatologist and was started on tapering doses of prednisone (total dose to be completed about 3 weeks later). She felt the rash was getting a little better; however, when the dose was tapered down to 20 mg, the rash worsened with a new burning sensation. She returned to the ER and was admitted about two weeks after starting the prednisone.

Her vital signs were stable. Temperature was 98.2°F, blood pressure was 122/69 mm Hg, heart rate was 82 beats per minute, and respiratory rate was 20. She appeared comfortable. Physical examination was remarkable for a diffuse, non-tender, non-blanching, maculo-papular wine-colored purpuric rash over the lower extremities, left upper extremity, and buttocks. Koebner's phenomenon was seen on the arm and left buttock (erythematous streaks accentuating the rash as a result of any irritation, including scratching).

Blood tests revealed white blood cell count to be 18 (4.5–11.0 K/mcL), hemoglobin 13 (12.0–16.0 g/dL), hematocrit 39.1 (37.0–47.0%), platelet count 461 (130–400 K/mcL), erythrocyte sedimentation rate 12 (0–20 mm/hr), prothrombin time 12.6 (11.5–13.1 sec), and partial thromboplastin time PTT: 26.7 (22.5–32.7 sec). Electrolytes, liver function tests and urine analysis were all normal. Additional studies include: rheumatoid factor <20 (0–20 IU/mL), antinuclear antibody, Anti-dsDNA, SS-A (Ro), SS-B (La), Smith, and RNP antibodies were all negative. Serum complements C3, C4 and CH50 were normal. Cryoglobulins, HBCore Ab IgM, HbsAb, HbsAg , and HCV antibodies were negative. Anti-proteinase-3 was 0 (<2 EU/mL), and anti-Myeloperoxidase Ab 6 (<6 EU/mL).

Esophagogastroduodenoscopy done for complaints of nausea and epigastric discomfort was normal. Patient was discharged 3 days later, receiving prednisone 30 mg daily. Follow-up in Rheumatology Clinic showed improvement of lesions on the legs; however, a new area of rash was developing on her left arm. Earlier the same week, the dermatologist had increased prednisone to 60 mg daily.

Conclusion: This is a classic case of hypersensitivity vasculitis. At this time, the patient has no evidence of internal organ involvement. She will continue to be followed by both Dermatology and Rheumatology clinics to monitor for internal organ involvement.

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Comparison of Baseline Troponin-I Levels in Patients with Normal vs. Impaired Renal Function. S. Pandey, D. Patel, B. Weiner, and D. Flores. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: The diagnostic value of cardiac troponin-I levels in suspected acute coronary syndromes in patients with abnormal renal function has always been controversial. Renal dysfunction may alter their sensitivity since their clearance appears to be renally dependent.

Objective: To compare baseline troponin-I levels in patients with normal renal function versus those with acute (ARF) and chronic (CRF) renal failure.

Design: There were 291 patients enrolled in a retrospective study: 100 patients with normal renal function, 91 patients with ARF, and 100 patients with CRF. In the first arm of the study, baseline troponin-I levels at the time of admission were drawn in these patients. Patients were further subdivided based upon cardiac versus non-cardiac admitting diagnoses. In the second arm of the study, the patients' troponin-I levels were mapped to determine whether or not their levels were in the range significant for an acute myocardial event in all groups.

Patients: Patients were selected randomly from admissions to a community hospital from January 2002 to March 2004. Patients with cardiac arrest were excluded from the study as resuscitation efforts may falsely elevate troponin levels.

Results: In the first arm of the study, mean troponin-I levels in cardiac versus non-cardiac patients were 0.405 and 0.1 in the normal renal function group respectively, 3.272 and 1.206 in the ARF group respectively, and 1.304 and 2.569 in the CRF group respectively. In the second arm of the study, the number of patients that had troponin elevations significant for an acute myocardial event in the cardiac versus non-cardiac group were 5 and 1 for those with normal renal function respectively, 6 and 13 for those with ARF respectively, and 5 and 17 for those with CRF respective.

Conclusion: Patients with CRF admitted for non-cardiac diagnoses had higher baseline troponin-I levels than did their cardiac counterparts. Moreover, CRF pts with non-cardiac admitting diagnoses had more troponin-I elevations consistent with acute myocardial events. Although troponin-I levels are routinely used in the diagnosis of acute coronary syndromes, their utility appears to be diminished in renally impaired patients.

How Well Are Healthcare Professionals Aware of the Costs of Various Laboratory and Radiological Tests? A Randomized Survey. C. Rathnakumar, A. Devarajan, N. Maddukuri, and J. Matta. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Background: Although the rising costs of healthcare are well known, many physicians, particularly residents in training, are not well aware of the costs of the tests that they are requesting. Improper understanding of the costs of tests can contribute to unnecessarily increased costs of care.

Materials and Methods: All residents and attending physicians of the Department of Medicine at Jersey City Medical Center will receive a fully formatted awareness survey to complete on the spot and return. The survey will include questions assessing their awareness of the costs of selected, commonly requested laboratory and radiology tests.

Results: The survey results are pending for statistical analysis by SAS program. Data will be analyzed for statistical significance and differences between attending physicians and residents.

Conclusions: The purpose of this study is to assess the awareness of the respondents, and also to impress upon the respondents the financial implications of test ordering. The study results will be available to the respondents once the statistical analysis of the data is completed.

An Unusual Presentation of a Rare Disease—Non-Hodgkin's Lymphoma of the Vagina.
G. Vu, C. Liburd, L.G. Hu, and S. Nayak. Department of Obstetrics and Gynecology, Jersey City Medical Center, Jersey City, NJ.

Introduction: Primary Non-Hodgkin's Lymphoma (NHL) of the vagina is a very rare malignancy. NHL can involve extranodal sites, primarily the gastrointestinal tract and the skin. Involvement of the female genital tract is most often secondarily involved in cases of disseminated disease.

Case: A 56 y.o. G3P3 post-menopausal morbidly obese woman presented with a day history of severe, constant, right lower quadrant and right flank pain, with difficulty urinating. Pelvic exam disclosed age-appropriate external genitalia with a normal appearing vagina and cervix. Bimanual exam was limited due to patient's body habitus, but induration was noted throughout the vaginal walls and cervix. Imaging studies showed "fat streaking" in the right adnexal area and pararectal tissues with moderate right hydronephrosis and hydroureter. Pap smear, endocervical curettage and endometrial biopsy were within normal limits. Vaginal biopsies revealed sclerosing large B-cell lymphoma.

Discussion: NHLs are lymphoid malignancies with an incidence of 57,000 cases and 26 deaths per year in the US. Age at diagnosis is 36 to 82 years of age. NHL of the vagina and cervix account for <1% of these cases. The most common presentation is vaginal bleeding, but NHL of the vagina may present as a mass, urinary frequency/pain, vaginal discharge or dysparuenia. Primary vaginal NHLs are clinically difficult to differentiate from inflammatory diseases or vaginal cancer. A thorough pelvic exam, a high index of suspicion, and liberal biopsies of indurated areas are necessary for prompt diagnosis and treatment.

A Case Report of Disseminated Cryptococcosis Presenting as Abdominal Pain. C. Tadros, R. Blejeru, J. Patel, S. Pandey, P. Joshi, M. Fernandez, and L. Tacsa. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Introduction: Disseminated crytococcosis affects mostly the central nervous system, lungs and skin. We present a rare instance of disseminated cryptococcosis as the etiology of erosive gastritis and fevers of unknown origin (FUO) in a patient with advanced AIDS.

Case Report: A 47-year-old male was admitted for vague left-sided abdominal pain associated with diarrhea and fever for 3 months. Pain was sharp, non-radiating, not associated with eating, moving bowels, or position. No urinary symptoms, nausea or vomiting, melena, or any other complaints were present. No history of HIV infection or opportunistic infections was obtained. On examination, patient was febrile to 102°F, wasted with oral thrush; cervical bilateral non-tender lymph nodes were present, and lungs were clear. Abdomen was unremarkable except for splenomegaly. No skin lesions or meningeal signs were noted. HIV test was positive and CD4=2. Chest x-ray was normal. Blood cultures including AFB were obtained and patient was started on empirical anti-MAC therapy with no change in symptoms. An upper endoscopy showed erosive gastritis; biopsies were positive for *C. neoformans*. After an initial unsuccessful course of IV Amphothericin B, patient was started on IV Fluconazole. Fever and abdominal pain subsided and patient was discharged on PO Fluconazole.

Discussion: We found only one prior report of disseminated cryptococcosis presenting with abdominal symptoms. Disseminated cryptococcosis should be considered in the differential of GI symptoms and FUO in an HIV infected patient, even in the absence of meningeal or pulmonary symptoms.

Epidemiology of Common Infection by Clinical Locations at Jersey City Medical Center (JCMC) for a Two-Year Period (2002–2003). K. Subramanian[1], A. Grigoriu[1], C. Strand[2], and R. Guerrero[2]. Departments of [1]Medicine and [2]Pathology, Jersey City Medical Center, Jersey City, NJ.

Objective: To study the prevalence of different microbial pathogens in different clinical locations at JCMC for two-year period by analyzing the first isolates and comparing organism distribution by clinical location using lab computer data (SCC Palm Harbor, Florida).

Most Common Infections at Various Clinical Locations

MICU	SICU	NICU	OP	IP
CNS 19.8%	CNS 18.6%	CNS 31.6%	E. coli 30.7%	E. coli 16.8%
S. aureus 11.5%	Acinetobacter 10.8%	P. aeruginosa 12.7%	E. faecalis 12.7%	CNS 16.5%
E. coli 10.8%	E. faecalis 10.2%	S. marcescens 9.5%	C. albicans 9.6%	S. aureus 11.8%
P. aeruginosa 9.9%	P. aeruginosa 9.8%	S. aureus 7.2%	GBS 7.4%	E. faecalis 8.5%
C. albicans 9.1%	E. coli 9.1%	C. parapsilosis 5.4%	S. aureus 6.4%	P. aeuruginosa 7.2%

Discussion: The pattern of organisms seen in various clinical sites is useful in management of patients before definitive microbiologic results are available. Review of infections at JCMC shows that central nervous system infections are common in critical care unit patients and *E. coli* infections in outpatients and general hospital patients.

Guillain-Barré Syndrome (GBS) Associated with Isolation of Enterovirus in Cerebrospinal Fluid: A Rare Entity.

S. Soosaimickam, C. Rathnakumar, S. Beltran, and J. Matta. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Learning Objectives: Guillain-Barré Syndrome is an acute inflammatory demyelinating polyradiculoneuropathy. GBS is an autoimmune disorder and an acute infectious process precedes 75% of cases. GBS associated with isolation of an organism in cerebrospinal fluid is very rare. Hereby, we report a case of GBS associated with isolation of enterovirus in cerebrospinal fluid.

Case: A 41-year-old Hispanic male presented with progressive weakness and numbness of all four extremities of two weeks duration. On physical examination he was found to have ascending flaccid paresis and glove and stocking numbness. Cerebrospinal fluid analysis showed cytoalbuminic dissociation, classical of GBS, and CSF culture grew enterovirus. CT head was normal. EMG revealed 20% reduction in motor conduction and severe dysfunction of peripheral nerves. Based on the clinical presentation and CSF analysis, GBS was diagnosed and patient was treated with intravenous immunoglobulin with a good clinical improvement.

Discussion: Neurological manifestations of enterovirus infection include aseptic meningitis, poliomyelitis like paralysis, encephalitis, acute transverse myelitis, acute cerebellar ataxia, opso-myoclonus syndrome and benign intracranial hypertension and GBS. GBS has been attributed to enterovirus in the past, although the diagnosis in those cases was associated with serologic antibody. GBS associated with isolation in entrovirus in CSF, as in our case, is extremely rare.

The Pathogenic Microorganism Frequency and the Antibiogram in the Jersey City Medical Center Neonatal Intensive Care Unit (NICU) for a Two-Year Period.

J. Patel[1], C. Strand[2], S. Puvabanditsin[1], S. Alsheikh[1], and R. Guerrero[2]. Departments of [1]Pediatrics and [2]Pathology, Jersey City Medical Center, Jersey City, NJ.

Infection is the leading cause of neonatal mortality and morbidity in the NICU. We studied the frequency of specific microorganisms and the antibiogram of the first isolates, as recommended by the NCCLS, for the years 2002-2003 at Jersey City Medical Center.

The study data shows that Coagulase Negative Staphylococcus (CNS) represents 32.2% of the total isolates, followed by *Pseudomonas aeruginosa* (15.6%); *Serratis marcescens* (12.6%); *Staphylococcus aureus* (9.0%); *Enterococcus fecalis* (7.0%); *Enterobacter cloacae* (6.5%); *Escherichia coli* (5.5%) and others (11.6%).

Important observations based on this data are:

1. Oxacillin sensitivity for Coagulase Negative Staphylococcus is only 2% in NICU compared with 19% for the general hospital (excluding NICU).
2. Oxacillin sensitivity for *S. aureus* is 94% in NICU compared with 60% for the general hospital (excluding NICU).
3. Imipenem sensitivity for *P. aeruginosa* is 90% in NICU compared with 74% for the general hospital (excluding NICU).
4. *S. marcescens* frequency is 12.6% in NICU compared with 2.2% for the general hospital (excluding NICU)
5. There are only 3 fungal isolates for the years 2002–2003: *Candida guillilermondii* (2 cases); *Candida albicans* (1 case). Thus fungi are infrequent pathogens in the NICU.

Comparison of the Outpatient Antibiogram to the Inpatient Antibiogram at Jersey City Medical Center.

C. Tadros[1], R. Guerrero[2], A. Grigoriu[1], and C. Strand[2]. Departments of [1]Medicine and [2]Pathology, Jersey City Medical Center, Jersey City, NJ.

Introduction: As we move to a new hospital, we are looking at the bacteriology and antibiotic sensitivity in the old hospital over the period of the last two years.

Methods: We are using the antibiogram from January 2002 to December 2003 following the NCCLS guidelines (one isolate per patient stay, and separate inpatient from outpatient antibiogram).

Findings and Conclusions: The higher number of the majority of individual isolates in the hospital versus the outpatient setting may be related to several factors including underlying morbidity, instrumentation, antibiotic usage and procedures. However, the higher frequency of *Escherichia coli* in the outpatient setting may be explained by the high prevalence of urinary tract infection (UTI) as an outpatient diagnosis.

The higher level of resistance to various antibiotics by individual pathogens in the inpatient setting provides consistent biological support for the hypothesis of a causal relationship between antibiotic usage and resistance (i.e., fluroquinolones usage).

The low overall sensitivity of *E. coli* to Ampicillin may be attributed to the high volume of antibiotic usage for UTI in the community.

The similar rate of resistance to Methicillin of the *Staphylococcus aureus* in both settings confirms the prevalence of MRSA in the community.

We are looking forward to repeating this study in the environment of the new hospital.

Anticonvulsant Hypersensitivity Syndrome (AHS).

P. Sunkavalli, I. Belem, and E. Mangosing. Department of Pediatrics, Jersey City Medical Center, Jersey City, NJ.

Background: Anticonvulsant hypersensitivity syndrome is a potentially fatal but rare complication of anti-epileptic drugs whose chemical structure is based on an aromatic ring (carbamazepine, phenobarbital, phenytoin, and primidone). Its incidence is estimated to range from 1/1000–1/10,000 exposures. The condition commonly manifests as rash, fever, tender lymphadenopathy, hepatitis, and eosinophilia. The condition can occur in any age group, but has most frequently been described in the adult population. Diagnosis in the pediatric patient is often complicated by the fact that fever, rash, and lymphadenopathy are common nonspecific signs of illness in children. Delay in diagnosis and discontinuation of the causative drug may result in increased severity and duration of internal organ involvement. Cross-reactivity occurs between medications, and worsening with successive exposures is a key feature of AHS. The most common cause of death is hepatic failure.

Methods: A PubMed search was done using the keywords "anticonvulsant," "carbamazepine," and "hypersensitivity." Dermatologist and neurologist were consulted.

Results: A case of AHS is described. Investigators have reported epidemiological data and described the pathophysiology, diagnostic criteria, and management options.

Conclusions: Anticonvulsant hypersensitivity syndrome should be considered in any patient treated with phenytoin, carbamazepine or phenobarbital who presents with fever, rash or lymphadenopathy. The medication should be immediately discontinued pending investigation. Although the incidence of AHS is rare, early recognition of the condition is essential in order to prevent unnecessary morbidity and mortality.

Cryptococcemia and CD4+ T-lymphocytopenia in a Human Immunodeficiency Virus Seronegative Patient.

C. Rathnakumar, S. Soosaimanickam, and J. Matta. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Learning Objectives: Cryptococcosis is a systemic infection caused by the encapsulate yeast *Cryptococcus neoformans*. Its incidence is greatly increased in immuno-compromised patients, especially among patients with AIDS. We report a case of cryptococcemia and CD4+ T-lymphocytopenia in an HIV-negative patient.

Case: This is a 41-year-old Egyptian male, with chronic renal failure presumed to be secondary to lupus nephritis. The patient was on hydroxychloroquine and prednisone for one year and was dependant on hemodialysis. The patient presented with sepsis, and septic work-up revealed cryptococcemia in the absence of HIV. T-lymphocyte panel showed low CD4 cell count (31) and low CD4/CD8 ratio (0.66), mimicking HIV. The patient is being treated with Amphotericin B with no clinical improvement.

Discussion: CD4-T-lymphocytopenia in the absence of HIV infection is rare. Other than HIV, tuberculosis, organ transplantation, therapeutic doses of steroids, sepsis, burns, lymphoreticular malignancies, and chronic renal failure are the most common predisposing factors for CD4 T-lymphocytopenia. Long term corticosteroid use in the setting of chronic renal failure and autoimmune disorder has precipated the fungemia and CD4 T-lymphocytopenia in our patients. Corticosteroids have pleiotropic effects on immunity that account for life-threatening invasive fungal infections. As the severity of the fungal infection is associated with the intensity of corticosteroid therapy, it should be used judiciously.

Elevated Troponins Do Not Always Indicate Myocardial Ischemia. S. Soosaimanickan, P. Thiruwilwamala, N. Pichika, and R. Mikkilenini. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Learning Objective: Chest pain, leading to work-up of acute coronary syndrome, is a common presenting complaint to the ER. Elevated cardiac troponin levels (cTnl) are a critical part of the diagnostic criteria, in addition to clinical history and EKG. However, elevated troponins may result from other etiologies, potentially leading to unnecessary investigation.

Case Reports: We report a subset of 6 patients admitted for complaints of chest pain, who had elevated troponins in their cardiac injury panel. They were treated with oxygen, aspirin, nitrates, beta-blocker, heparin and Plavix. Subsequent work-up with EKG, echo, exercise / thallium stress test (2) and cardiac catheterization (2) showed no evidence of coronary artery disease. Out of the 6 patients, 2 had sepsis syndrome, 1 had subarachnoid hemorrhage, 1 had epidural hemorrhage and 2 had COPD with cor pulmonale.

Discussion: Cardiac troponin isomer cTnl is considered highly specific for acute coronary syndrome. But there are non-cardiac causes of elevated of cTnl, including pulmonary embolism, sepsis, subarachnoid hemorrhage, chemotherapy, renal failure, HIV, endurance exercise, etc. This study emphasizes that the whole clinical picture should be taken into consideration rather than just the serum markers

Colonoscopic Retrieval of an Intestinal Depot of Phencyclidine. S. Pandey, M. Fernandez, Y. Bains, D. Flores, T. Brannan, and C. Tadros. Department of Medicine, Jersey City Medical Center, Jersey City, NJ.

Phencyclidine is a hallucinogenic drug that is popular among drug dealers due to the fact that it is inexpensive and easy to manufacture. Toxic ingestions have resulted in a prolonged coma secondary to slow drug absorption caused by ruptured packets of ingested PCP in drug smugglers. Here we present a case where colonoscopy was utilized to remove multiple packets of PCP during a toxic ingestion with a rapid improvement in the patient's clinical condition post-procedure.

Case: A 21-year-old AAM presented to the ER with a seizure and respiratory distress. The patient was appearing in court and was expecting to receive a 9-month sentence. He has no medical history and was taking no medications. He was a heavy abuser of "angel dust" (PCP), "dip"(PCP), and "weed" (marijuana). In anticipation of his incarceration, the patient swallowed nine "balloons" of PCP and marijuana in order to sell them during his stay in prison. On arrival at the ER, he was in severe respiratory distress and was intubated for airway protection. BP was 125/73, P 131, RR 21 breaths/min, Temp 100.7°F. He was in severe respiratory distress, agitated, and combative. The physical examination was normal. Laboratory examinations revealed a total CPK of 3618, BUN 13, and creatinine 1.4. Toxicology screen was positive for benzodiazepines, cannabinoid, and PCP. The patient was admitted to the MICU and an EGD was performed which failed to locate their position. The patient was comatose with opisthotonic posturing and seizure-like contractions. On day #4, the patient had no bowel movements and therefore poison control was recontacted. They recommended an exploratory laparotomy. The procedure was performed on Day #5 and the bowel was milked four times with the packets being pushed to the rectosigmoid area. Serial rectal examinations performed throughout the night failed to reveal the packets, and therefore the patient underwent a colonoscopy on day #6. Six balloons were filled with PCP and a tobacco-like substance was retrieved colonoscopically with polypectomy snares. Once the packets were retrieved, the patient's clinical condition improved rapidly. He was extubated and regained consciousness within 24 hours.

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Author, Subject, Title Index to Volume 71

AAV vectors for hemophilia B gene therapy, H Chao, CE Walsh: 71(5):305–313
Abramson RG: Obituary: 71(5): inside back cover
Abscess drainage: 71(5):351–354
Abstracts: Annual Resident Research Day 2004—Jersey City Medical Center: 71(6):424–426
Abstracts: Research Day 2004—Queens Hospital Center: 71(6):419–424
Abstracts: Research in Medicine 2003—Jersey City Medical Center 71(3):209–211
Abstracts: Research in Medicine 2003—Queens Hospital Center 71(3):211–215
Abstracts: Research in Medicine 2004—Mount Sinai School of Medicine: 71(6):415–419
Academic health centers: 71(5):314–321
Acid-base: 71(4):281–284
Acidosis: 71(4):281–284
Acute coronary syndrome: 71(3):197–208; 71(6):375–383
Acute myocardial infarction and left subclavian artery occlusion in Behçet's disease: a case report, A Iyisoy, H Kursaklioglu, S Kose, Z Yesilova, C Ozturk, K Saglam, E Demirtas: 71(5):330–334
Adeno-associated virus: 71(5):305–313
Adhami N, Ahmed R, Lento PA, Shimshi M, Herman SD, Teirstein AS, Fibrous pleural tumor with hypoglycemia: case study: 71(5):344–346
Adjustable gastric band: 71(1):63–71
Adolescence: 71(3):155–161; 71(3):162–165
Adolescent females: 71(3):148–154
Adolescent health: 71(3):155–161; 71(3):162–165; 71(3):170–173; 71(3):181–185; 71(3):186–190; 71(3):191–196
Adolescent school-based health care: a description of two sites in their 20th year of service, DR Pastore, B Techow: 71(3):191–196
Adolescents: 71(3):148–154; 71(3):174–180
Adolescents and immunization: tips for the primary care provider, S Edwards, A Diaz: 71(3):162–165
African-American: 71(6): 368–374
Ahmed R: see Adhami N
Altruism: 71(4):251–254; 71(4):255–265
Alzheimer's disease: 71(1):55–62
Amebiasis: 71(5):347–350
Anagnostopoulos GK: see Pavlakis GM; see Sakorafas GH
Anand SX: see Viles-Gonzalez JF
Anchorage: 71(6):361–367
Aneurysm: 71(1):1–3; 71(1):12–16; 71(1):17–28
Anion gap: 71(4):281–284
Anoikis: 71(6):361–367
Anorexia nervosa: 71(3):155–161
Anti-arrhythmic agents: 71(1):47–54
Anticoagulation: 71(1):47–54; 71(5):322–329
Anticoagulation in pregnant women with prosthetic heart valves, S Danik, V Fuster: 71(5):322–329
Antiplatelet: 71(6):375–383
Antithrombotic therapy: 71(3):197–208
Apoptosis: 71(3):197–208
Aronson S, Where the wild things are: the power and challenge of adolescent group work: 71(3):174–180
Arterial trauma: 71(1):4–11
Arteriovenous malformations: 71(1):17–28; 71(1):29–41
Atherosclerosis: 71(3):197–208
Atherothrombosis: 71(3):197–208
Autopsy: 71(1):55–62
AV fistula:71(2):94–102

Bacon BR: see Hassan H0
Badimon JJ: see Viles-Gonzalez JF
Baily MA, Ethics, economics, and physician reimbursement: 71(4):231–235
Bariatric surgery: 71(1):63–71
Baron JH, If I were dean: a challenge to new medical students: 71(2):134–138; "Thou shalt not kill": some legal and linguistic problems: 71(5):355–357
Bastani B: see Hassan H
Bauer JJ: see Hazzan D
Behçet's disease: 71(5):330–334
Bennekov T, Spector D, Langhoff E, Induction of immunity against human cytomegalovirus: 71(2):86–93
Beta-blockers: 71(1):47–54
Betancourt JR, Maina AW, The Institute of Medicine Report "Unequal Treatment": implications for academic health centers: 71(5):314–321
Bias: 71(4):236–242
Biliopancreatic diversion: 71(1):63–71
Bioethics: 71(5):355–357
BiP: 71(5):289–297
BiP is a master regulator of the ER function, L Hendershot: 71(5):289–297
Bitterman J: see Diaz A
Bodenheimer HC Jr: see Lee CS
Book Reviews: Cardiac pacemakers step by step: an illustrated guide, D Mehta: 71(6):411; Peripheral vascular disease for cardiologists: a clinical approach, J Jang: 71(6):411–412; Health literacy: a prescription to end confusion, MH Savitz: 71(6):413; Pharmacy law digest, 39th edition, P Paxos: 71(6):413–414
Bosentan: 71(2):103–114
Brickman AM: see Samuels SC
Bulimia nervosa: 71(3):155–161
Burd JA: see Samuels SC
Burrows L, Selling organs for transplantation: 71(4):251–254
Business model: 71(4):225–230

Canada: 71(4):225–230
Cardiac pacemakers step by step: an illustrated guide, D Mehta: Book Review: 71(6):411
Cardiovascular disease: 71(6):375–383
Cardiovascular disease in diabetics: pharmacology and revascularization, SS Mangalmurti, ME Farkouh: 71(6):375–383
Carmel S: see Wenger NS
Carotid stenosis: 71(1):29–41
Carpal tunnel release: 71(6): 401–404
Carpal tunnel release: using a short vertical incision above the flexor crease of the wrist, A Dayican, VS Unal, S Portakal, A Utkan, MA Tumoz: 71(6): 401–404
Carpal tunnel syndrome: 71(6): 401–404
Carroccio A, Spielvogel D, Combined open and endovascular techniques for the treatment of complex vascular disease: 71(1):12–16
Catheter:71(2):94–102
Chao H, Walsh CE, AAV vectors for hemophilia B gene therapy: 71(5):305–313
Chapman M: see Hazzan D
Children's Aid Society: 71(3):166–169
CHIP: 71(3):186–190
CHIP: new opportunities in adolescent health care delivery, A Diaz, S Edwards, WP Neal, P Ludmer, J Bitterman, AT Nucci: 71(3):186–190
Chronic disease: 71(6): 368–374
Chronic heart failure: 71(2):115–126
Circulation: 71(4):274–280
Cirrhosis: 71(4):281–284
Clinical research: 71(4):266–270
Clinical trials: 71(5):298–304
Coercion: 71(4):255–265
Colitis: 71(5):347–350
Colon B: see Diaz A
Combined open and endovascular techniques for the treatment of complex vascular disease, A Carroccio, D Spielvogel: 71(1):12–16
Commodification: 71(4):255–265
Community: 71(6): 368–374
Community-based participatory research: 71(6): 368–374
Compassion: 71(2):134–138

Compensation: 71(4):266–270
Competition: 71(4):219–224
Complications: 71(5):351–354
Compression: 71(4):285–286
Compression of the radial branch of the median nerve due to an anomalous muscle belly of the first lumbrical in a child, ME Pruzansky: 71(4):285–286
Conflict of interest: 71(4):236–242; 71(4):266–270
Coronary artery disease: 71(3):197–208
Crohn's disease: 71(5):351–354
Current medical treatment of pulmonary arterial hypertension, R Sulica, M Poon: 71(2):103–114
Cytomegalovirus: 71(2):86–93; 71(5):347–350
Cytomegalovirus colitis in an immunocompetent patient with amebiasis: case report and review of the literature, CS Lee, AH Low, PT Ender, HC Bodenheimer, Jr: 71(5):347–350

Danik S, Fuster V, Anticoagulation in pregnant women with prosthetic heart valves: 71(5):322–329
Dayican A, Unal VS, Portakal S, Utkan A, Tumoz MA, Carpal tunnel release: using a short vertical incision above the flexor crease of the wrist: 71(6): 401–404
Dean's Lectures: BiP is a master regulator of the ER function, L Hendershot: 71(5):289–297; Molecular signaling regulating anchorage-independent growth of cancer cells, L-H Wang: 71(6):361–367
Delogu AB: see Rigante D
Dementia: 71(1):55–62
Demirtas E: see Iyisoy A
Dendritic cells: 71(2):86–93
Depression: 71(1):55–62
Depression in autopsy-confirmed dementia with Lewy bodies and Alzheimer's disease, SC Samuels, AM Brickman, JA Burd, Dushyant P. Purohit, PQ Qureshi, M Serby: 71(1):55–62
De Rosa G: see Rigante D
Desmoid tumors: 71(6): 384–391
Devereaux PJ: see Guyatt GH
Diabetes: 71(6):375–383
Diagnosis: 71(2):73–85
Dialysis:71(2):94–102
Diaz A, Edwards S, Neal WP, Elbirt P, Rappaport M, Kierstead R, Colon B, Foster children with special needs: The Children's Aid Society experience.71(3):166–169
Diaz A, Edwards S, Neal WP, Ludmer P, Bitterman J, Nucci AT, CHIP: New opportunities in adolescent health care delivery: 71(3):186–190
Diaz A, Edwards S, Neal WP, Ludmer P, Sondike SB, Kessler C, Medeiros D, Nucci AT, Obtaining a history of sexual victimization from adolescent females seeking routine health care: 71(3):170–173
Diaz A, Introduction: the Mount Sinai Adolescent Health Center: 71(3):146–147
Diaz A, Neal WP, Nucci AT, Ludmer P, Bitterman J, Edwards S, Legal and ethical issues facing adolescent health care professionals: 71(3):181–185
Diaz A: see Edwards S; see Siqueira LM
Digitalis: 71(1):47–54
Direct payments: 71(4):219–224 Drug testing: 71(4):266–270
Distal revascularization interval ligation: 71(2):94–102
Doppler ultrasound: 71(2):94–102
Dyslipidemia: 71(6):375–383

Early reactions to Harvey's circulation theory: the impact on medicine, SA Lubitz: 71(4):274–280
Eating disorders: 71(3):155–161
Ectopic intrathoracic goiter: 71(2):131–133
Ectopic intrathoracic thyroid: case report, GH Sakorafas, A Vlachos, G Tolumis, GA Kassaras, GK Anagnostopoulos, D Gorgogiannis: 71(2):131–133
Edwards S, Diaz A, Adolescents and immunization: tips for the primary care provider: 71(3):162–165
Edwards S: see Diaz A
Egg donation: 71(4):255–265
Eighty hours a week: a third-year resident's perspective on duty-hour limitations, Sl Shah: 71(5):358–360
Elias SM, Frasier KL, Minimally invasive vein surgery: 71(1):42–46
Elbirt P: see Diaz A
Elite: 71(4):219–224
Embolization: 71(1):17–28; 71(1):29–41
Embolization of complex vascular lesions, RA Lookstein, J Guller: 71(1):17–28
End of life decisions: 71(5):335–343
End points: 71(5):298–304
Ender PT: see Lee CS
Endograft: 71(1):12–16
Endoleak: 71(1):17–28
Endothelial dysfunction: 71(3):197–208
Endothelin receptor antagonist: 71(2):103–114
Endovascular techniques: 71(1):12–16
Endovascular therapy: 71(1):29–41
Endovascular therapy for the treatment of arterial trauma, CS McArthur, ML Marin: 71(1):4–11
Endovascular treatment: 71(1):1–3; 71(1):4–11
Endovascular treatment of neurovascular disorders, AB Patel, DM Johnson: 71(1):29–41
Endovascular treatment of peripheral arterial aneurysms, NJ Morrissey: 71(1):1–3
Epoprostenol: 71(2):103–114
ER chaperones: 71(5):289–297
ER stress: 71(5):289–297
Ethical differences between socialized and HMO systems, Guest Editors: MH Savitz, MM Rivlin: 71(6): 392–400
Ethics: 71(3):162–165; 71(3):170–173; 71(3):181–185; 71(3):186–190; 71(4):243–250; 71(4):251–254; 71(4):255–265; 71(4):266–270; 71(6): 392–400
Ethics, economics, and physician reimbursement, MA Baily: 71(4):231–235
Ethics in the marketing of medical services, SR Latham: 71(4):243–250
Ethnic disparities: 71(5):314–321
Ethnic minorities: 71(5):314–321
Evaluation of serum anion gap in patients with liver cirrhosis of diverse etiologies, H Hassan, JH Joh, BR Bacon, B Bastani: 71(4):281–284
Exercise: 71(1):47–54
Exploitation: 71(4):255–265

Falk A: see Vassalotti JA
Familial adenomatous polyposis: 71(6): 384–391
Familial polyposis coli: clinical manifestations, evaluation, management and treatment, G Nandakumar, JA Morgan, D Silverberg, RM Steinhagen: 71(6):384–391
Families: 71(4):255–265
Farkouh ME: see Mangalmurti SS
Federico G: see Rigante D
Fee-for-service: 71(4):231–235
Fees: 71(4):219–224; 71(4):236–242
Fibrous pleural tumor with hypoglycemia: case study, N Adhami, R Ahmed, PA Lento, M Shimshi, SD Herman, AS Teirstein: 71(5):344–346
Fiduciary responsibility: 71(4):236–242
Financial remuneration: 71(4):251–254
Fishman E: see Hazzan D
Foster care adolescent health: 71(3):166–169
Foster care children: 71(3):166–169
Foster children with special needs: The Children's Aid Society experience. A Diaz, S Edwards, WP Neal, P Elbirt, M Rappaport, R Kierstead, B Colon: 71(3):166–169
Fostering resilience in adolescent females, LM Siqueira, A Diaz: 71(3):148–154
Frasier KL: see Elias SM
Fuster V: see Viles-Gonzalez JF, see Danik S

Gardner: 71(6): 384–391
Gastric bypass: 71(1):63–71
Gastrointestinal bleeding: 71(2):127–130
Gene therapy: 71(5):305–313

Gene transduction: 71(2):86–93
Gilbert HS: Obituary: 71(1):72
Goiter: 71(2):131–133
Gorgogiannis D: see Sakorafas GH
Graft:71(2):94–102
Grand Rounds: A review of heart failure treatment, GH Guyatt, PJ Devereaux: 71(1):47–54; Renal artery disease: diagnosis and management, JW Olin: 71(2):73–85; Induction of immunity against human cytomegalovirus, T Bennekov, D Spector, E Langhoff: 71(2):86–93; Multidisciplinary approach to hemodialysis vascular access at The Mount Sinai Hospital, the, JA Vassalotti, A Falk, V Teodorescu, J Uribarri: 71(2):94–102; Current medical treatment of pulmonary arterial hypertension, R Sulica, M Poon: 71(2):103–114; Neurohormonal antagonism in heart failure: what is the optimal strategy? JD Sackner-Bernstein, D Hart: 71(2):115–126; Update in atherothrombotic disease, JF Viles-Gonzalez, SX Anand, C Valdiviezo, MU Zafar, R Hutter, J Sanz, T Rius, M Poon, V Fuster, JJ Badimon: 71(3):197–208; Measurement of end points in heart failure trials: jousting at windmills? PJ Hauptman: 71(5):298–304; AAV vectors for hemophilia B gene therapy, H Chao, CE Walsh: 71(5):305–313; The Institute of Medicine report "Unequal Treatment": implications for academic health centers, JR Betancourt, AW Maina: 71(5):314–321; Anticoagulation in pregnant women with prosthetic heart valves, S Danik, V Fuster: 71(5):322–329; Using community-based participatory research to reduce health disparities in East and Central Harlem, C Horowitz: 71(6):368–374; Cardiovascular disease in diabetics: pharmacology and revascularization, SS Mangalmurti, ME Farkouh: 71(6):375–383
Grants: 71(6): 368–374
Group therapy work: 71(3):174–180
Guller J: see Lookstein RA
Guyatt GH, Devereaux PJ, A review of heart failure treatment: 71(1):47–54

Hart D: see Sackner-Bernstein JD
Harvey, William: 71(4):274–280
Hassan H, Joh JH, Bacon BR, Bastani B, Evaluation of serum anion gap in patients with liver cirrhosis of diverse etiologies: 71(4):281–284
Hauptman PJ, Measurement of end points in heart failure trials: jousting at windmills? 71(5):298–304
Hazzan D, Fishman E, Heller E, Chapman M, Bauer JJ, Liver abscess in Crohn's disease: a report of three cases: 71(5):351–354
Health care: 71(4):243–250; 71(5):314–321
Health disparities: 71(6): 368–374
Health insurance: 71(3):186–190
Health literacy: a prescription to end confusion, MH Savitz: Book Review: 71(6):413
Healthy volunteers: 71(4):266–270
Heart failure: 71(1):47–54; 71(5):298–304
Heller E: see Hazzan D
Hemophilia B: 71(5):305–313
Hendershot L, BiP is a master regulator of the ER function: 71(5):289–297
Hepatotoxicity: 71(6):405–410
Hereditary colon cancer: 71(6): 384–391
Herman SD: see Adhami N
Herron DM, Surgical management of severe obesity: 71(1):63–71
HIPAA: 71(4):236–242
History of medical payments: continuity or crisis? DA Valone: 71(4):219–224
History of medicine: 71(4):219–224
HMO: 71(6): 392–400
Horowitz C, Using community-based participatory research to reduce health disparities in East and Central Harlem: 71(6): 368–374
Hutter R: see Viles-Gonzalez JF
Hypertension: 71(6):375–383
Hypoglycemia: 71(5):344–346

If I were dean: a challenge to new medical students, JH Baron: 71(2):134–138
Iliac arteries: 71(1):12–16
Immunity: 71(2):86–93
Immunization: 71(3):162–165
Immunocompetent: 71(5):347–350
Imperfect information: 71(4):231–235
Incentives: 71(4):225–230
Inducement: 71(4):266–270
Induction of immunity against human cytomegalovirus, T Bennekov, D Spector, E Langhoff: 71(2):86–93
Inflammation: 71(3):197–208
Inflammatory bowel disease: 71(5):351–354
Informed consent: 71(4):255–265
Institute of Medicine Report "Unequal Treatment": implications for academic health centers, JR Betancourt, AW Maina: 71(5):314–321
Insulin resistance: 71(6):375–383
Insurance: 71(4):231–235
Interferon gamma: 71(2):139–142
Intestinal metastases from renal cell carcinoma: a rare cause of intestinal obstruction and bleeding, GM Pavlakis, GH Sakorafas, GK Anagnostopoulos: 71(2):127–130
Intracranial aneurysms: 71(1):29–41
Intracranial stenosis: 71(1):29–41
Introduction: issues in medical ethics: mixing money and medicine, R Rhodes, DA Moros: 71(4):217–218
Introduction: the Mount Sinai Adolescent Health Center, A Diaz: 71(3):146–147
Iyisoy A, Kursaklioglu H, Kose S, Yesilova Z, Ozturk C, Saglam K, Demirtas E, Acute myocardial infarction and left subclavian artery occlusion in Behçet's disease: a case report: 71(5):330–334

Jahn A, Letter to the editor: 71(4): 287–288
Jang J, Peripheral vascular disease for cardiologists: a clinical approach: book review: 71(6):411–412
Joh JH: see Hassan H
Johnson DM: see Patel AB

Kaplan Seidenfeld ME, Sosin E, Rickert VI, Nutrition and eating disorders in adolescents: 71(3):155–161
Kassaras GA: see Sakorafas GH
Kaya M: see Satar S
Kessler C: see Diaz A
Kierstead R: see Diaz A
Kose S: see Iyisoy A
Koseoglu Z: see Satar S
Kupfer S: Obituary: 71(1):inside front cover
Kursaklioglu H: see Iyisoy A

Langhoff E: see Bennekov T
Latham SR, Ethics in the marketing of medical services: 71(4):243–250
Latino: 71(6): 368–374
Lee CS, Low AH, Ender PT, Bodenheimer HC Jr, Cytomegalovirus colitis in an immunocompetent patient with amebiasis: case report and review of the literature: 71(5):347–350
Legal and ethical issues facing adolescent health care professionals, A Diaz, WP Neal, AT Nucci, P Ludmer, J Bitterman, S Edwards: 71(3):181–185
Legal issues: 71(3):181–185
Lento PA: see Adhami N
Letters to the Editor: Jahn A: 71(4):287–288; Shah SI: 71(5):358–360
Lewy bodies: 71(1):55–62
Liver: 71(6):405–410
Liver abscess in Crohn's disease: a report of three cases, D Hazzan, E Fishman, E Heller, M Chapman, JJ Bauer: 71(5):351–354
Lookstein RA, Guller J, Embolization of complex vascular lesions: 71(1):17–28
Low AH: see Lee CS
Lubitz SA, Early reactions to Harvey's circulation theory: the impact on medicine: 71(4):274–280
Ludmer P: see Diaz A
Lumbrical: 71(4):285–286

Maina AW: see Betancourt JR
Managed care: 71(4):225–230
Mandated reporting: 71(3):181–185
Mangalmurti SS, Farkouh ME, Cardiovascular disease in diabetics: pharmacology and revascularization: 71(6):375–383
Marin ML: see McArthur CS
Market competition: 71(4):243–250
Matthews M, Jr., Medicine as a business: 71(4):225–230
McArthur CS, Marin ML, Endovascular therapy for the treatment of arterial trauma: 71(1):4–11
Measurement of end points in heart failure trials: jousting at windmills? PJ Hauptman: 71(5):298–304
Medeiros D: see Diaz A
Median: 71(4):285–286
Median nerve entrapment: 71(6): 401–404
Medical economics: 71(4):231–235
Medical ethics: 71(4):231–235; 71(6): 392–400
Medical history: 71(4):274–280
Medical marketing: 71(4):243–250
Medical markets: 71(4):231–235
Medical savings accounts: 71(4):225–230
Medical students: 71(2):134–138
Medicine as a business M Matthews, Jr.: 71(4):225–230
Mehta D, Cardiac pacemakers step by step: an illustrated guide: book review: 71(6):411
Minimally invasive surgery: 71(1):42–46
Minimally invasive vein surgery, SM Elias, KL Frasier: 71(1):42–46
Minority health: 71(5):314–321
Molecular signaling regulating anchorage-independent growth of cancer cells, L-H Wang: 71(6): 361–367
Morbid obesity: 71(1):63–71
Morgan JA: see Nandakumar G
Moros DA: see R Rhodes
Morrissey NJ, Endovascular treatment of peripheral arterial aneurysms: 71(1):1–3
Multidisciplinary approach to hemodialysis vascular access at The Mount Sinai Hospital, JA Vassalotti, A Falk, V Teodorescu, J Uribarri: 71(2):94–102
Murder: 71(5):355–357
Myocardial infarction: 71(5):330–334; 71(6):375–383

Nandakumar G, Morgan JA, Silverberg D, Steinhagen RM, Familial polyposis coli: clinical manifestations, evaluation, management and treatment: 71(6): 384–391
Neal WP: see Diaz A
Need: 71(4):231–235
Nerve: 71(4):285–286
Neurohormonal antagonism in heart failure: what is the optimal strategy? JD Sackner-Bernstein, D Hart: 71(2):115–126
Nonspecific interstitial pneumonia: 71(2):139–142
Nucci AT: see Diaz A
Nutrition: 71(3):155–161
Nutrition and eating disorders in adolescents, ME Kaplan Seidenfeld, E Sosin, VI Rickert: 71(3):155–161

Obesity: 71(1):63–71
Obituaries: Sherman Kupfer, M.D.: 71(1):inside front cover; Harriet S. Gilbert, M.D.: 71(1):72; Ruth Gail Abramson, M.D.: 71(5): inside back cover; Ezra M. Greenspan, M.D.: 71(6): inside back cover
Obtaining a history of sexual victimization from adolescent females seeking routine health care, A Diaz, S Edwards, WP Neal, P Ludmer, SB Sondike, C Kessler, D Medeiros, AT Nucci: 71(3):170–173
Olin JW, Renal artery disease: diagnosis and management: 71(2):73–85
Open surgical reconstruction: 71(1):12–16
Organ donation: 71(6): 392–400
Organophosphate: 71(6):405–410
Organs: 71(4):251–254
Ozturk C: see Iyisoy A

PI3 kinase: 71(6):361–367
Panel discussion: 71(4):271–273
Pastore DR, Techow B, Adolescent school-based health care: a description of two sites in their 20th year of service: 71(3):191–196
Patel AB, Johnson DM, Endovascular treatment of neurovascular disorders: 71(1):29–41
Patient confidentiality: 71(3):181–185
Pavlakis GM, Sakorafas GH, Anagnostopoulos GK, Intestinal metastases from renal cell carcinoma: a rare cause of intestinal obstruction and bleeding: 71(2):127–130
Paxos P, Pharmacy law digest, 39th edition: book review: 71(6):413–414
Payment: 71(4):219–224; 71(4):255–265; 71(4):251–254
Payment for egg donation and surrogacy, B Steinbock: 71(4):255–265
Pediatric: 71(4):285–286
Pediatrics: 71(2):139–142
Pentz RD, Spreading it around: money for researchers and subjects: 71(4):266–270
Peripheral arterial aneurysm: 71(1):1–3
Peripheral vascular disease for cardiologists: a clinical approach, J Jang: Book Review: 71(6):411–412
Pharmaceutical research: 71(4):266–270
Pharmacy law digest, 39th edition, P Paxos: book review: 71(6):413–414
Phase I trials: 71(4):266–270
Physician-assisted suicide: 71(6): 392–400
Physician behavior: 71(5):335–343
Physician-patient relationship: 71(4):231–235; 71(4):236–242
Physicians' religiosity and end-of-life care attitudes and behaviors, NS Wenger, S Carmel: 71(5):335–343
Placement: 71(4):243–250
Pleura: 71(5):344–346
Poisoning: 71(6):405–410
Poon M: see Sulica R; see Viles-Gonzalez JF
Poor, the: 71(4):219–224
Portakal S: see Dayican A
Pralidoxime: 71(6):405–410
Pregnancy: 71(5):322–329
Presumed consent: 71(4):251–254
Price: 71(4):243–250
Primary pulmonary hypertension: 71(2):103–114
Product: 71(4):243–250
Professional journals: 71(4):236–242
Professionalism: 71(4):243–250
Promotion: 71(4):243–250
Prostacyclin: 71(2):103–114
Prosthetic heart valves: 71(5):322–329
Protective factors: 71(3):148–154
Pruzansky ME, Compression of the radial branch of the median nerve due to an anomalous muscle belly of the first lumbrical in a child: 71(4):285–286
Pseudo-science: 71(2):134–138
Pulmonary arterial hypertension: 71(2):103–114
Purohit DP: see Samuels SC

Qureshi PQ: see Samuels SC

Racial disparities: 71(5):314–321
Racial minorities: 71(5):314–321
Randomized controlled trials: 71(1):47–54
Rappaport M: see Diaz A
Rationing: 71(4):225–230; 71(6): 392–400
Recombinant interferon gamma-lb and low-dose steroid in two pediatric cases of nonspecific interstitial pneumonia, D Rigante, AB Delogu, G Federico, G De Rosa, A Stabile: 71(2):139–142
Regulation: 71(4):219–224
Reproductive technology: 71(6): 392–400
Reimbursement: 71(4):231–235
Religion: 71(5):335–343; 71(5):355–357
Renal artery disease: 71(2):73–85
Renal artery disease: diagnosis and management, JW Olin: 71(2):73–85
Renal cell carcinoma: 71(2):127–130

Resilience: 71(3):148 – 154
Retrosternal goiter: 71(2):131 – 133
Revascularization: 71(6):375 – 383
Review of heart failure treatment, a, GH Guyatt, PJ Devereaux: 71(1):47 – 54
Rho GTPases: 71(6):361 – 367
Rhodes R, Moros DA, Introduction: issues in medical ethics: mixing money and medicine: 71(4):217 – 218
Rickert VI: see Kaplan Seidenfeld ME
Rigante D, Delogu AB, Federico G, De Rosa G, Stabile A, Recombinant interferon gamma-lb and low-dose steroid in two pediatric cases of nonspecific interstitial pneumonia: 71(2):139 – 142
Risk factors: 71(3):148 – 154
Rius T: see Viles-Gonzalez JF
Rivlin MM: see Savitz MH
Rush, Benjamin: 71(4):219 – 224

Sackner-Bernstein JD, Hart D, Neurohormonal antagonism in heart failure: what is the optimal strategy? 71(2):115 – 126
Saglam K: see Iyisoy A
Sakorafas GH: see Pavlakis GM
Sakorafas GH, Vlachos A, Tolumis G, Kassaras GA, Anagnostopoulos GK, Gorgogiannis D, Ectopic intrathoracic thyroid: case report: 71(2):131 – 133
Salaried practice: 71(4):231 – 235
Samuels SC, Brickman AM, Burd JA, Purohit DP, Qureshi PQ, Serby M, Depression in autopsy-confirmed dementia with Lewy bodies and Alzheimer's disease: 71(1):55 – 62
Sanz J: see Viles-Gonzalez JF
Satar D: see Satar S
Satar S, Satar D, Tap O, Koseoglu Z, Kaya M, Ultrastructural changes in rat liver treated with pralidoxime following acute organophosphate poisoning: 71(6):405 – 410
Savitz MH, Health literacy: a prescription to end confusion: Book Review: 71(6):413
Savitz MH, Rivlin MM, Guest Editors, Ethical differences between socialized and HMO systems: 71(6): 392 – 400
School-based health: 71(3):191 – 196
School health programs: 71(3):191 – 196
Science: 71(2):134 – 138
Scientific method: 71(4):274 – 280
Secretory pathway: 71(5):289 – 297
Self-management: 71(6): 368 – 374
Selling organs for transplantation, L Burrows: 71(4):251 – 254
Serby M: see Samuels SC
Serotype: 71(5):305 – 313
Severe obesity: 71(1):63 – 71
Sexual abuse: 71(3):170 – 173
Sexual victimization: 71(3):170 – 173
Shah SI, Eighty hours a week: a third-year resident's perspective on duty-hour limitations: 71(5):358 – 360
Shimshi M: see Adhami N
Silverberg D: see Nandakumar G
Single payer: 71(4):225 – 230
Siqueira LM, Diaz A, Fostering resilience in adolescent females: 71(3):148 – 154
Small bowel obstruction: 71(2):127 – 130
Socialized medicine: 71(6): 392 – 400
Sondike SB: see Diaz A
Sosin E: see Kaplan Seidenfeld ME
Spector D: see Bennekov T
Spreading it around: money for researchers and subjects, RD Pentz: 71(4):266 – 270
Stabile A: see Rigante D
Stat3: 71(6):361 – 367
Static venous pressure: 71(2):94 – 102
Steinbock B, Payment for egg donation and surrogacy: 71(4):255 – 265
Steinhagen RM: see Nandakumar G
Stell LK, Two cheers for physicians' conflicts of interest: 71(4):236 – 242
Stent-grafting: 71(1):4 – 11
Steroid: 71(2):139 – 142
Stroke: 71(1):29 – 41
Subclavian artery occlusion: 71(5):330 – 334
Sulica R, Poon M, Current medical treatment of pulmonary arterial hypertension: 71(2):103 – 114
Surgery: 71(5):351 – 354
Surgical management of severe obesity, DM Herron: 71(1):63 – 71

Tap O: see Satar S
Techow B: see Pastore DR
Teirstein AS: see Adhami N
Teodorescu V: see Vassalotti JA
Terminal care: 71(5):335 – 343
Theme Issues: Minimally invasive vascular surgery: the evolution of endovascular therapy, Part 2: 71(1)1 – 46; Adolescent medicine: 71(3):146 – 208; Medicine, money and morals: 71(4):217 – 273
Thoracic aorta: 71(1):12 – 16
"Thou shalt not kill": some legal and linguistic problems, JH Baron: 71(5):355 – 357
Thrombolysis: 71(1):29 – 41; 71(2):94 – 102
Thyroidectomy: 71(2):131 – 133
Tissue factor: 71(3):197 – 208
Tolumis G: see Sakorafas GH
Transplant: 71(4):251 – 254
Treatment: 71(2):73 – 85; 71(2):103 – 114; 71(2):115 – 126; 71(6):405 – 410
Treprostinil: 71(2):103 – 114
Triage: 71(6): 392 – 400
Trust: 71(4):236 – 242
Tumor: 71(5):344 – 346
Tumoz MA: see Dayican A
Two cheers for physicians' conflicts of interest, LK Stell: 71(4):236 – 242

Ultrastructural changes in rat liver treated with pralidoxime following acute organophosphate poisoning, S Satar, D Satar, O Tap, Z Koseoglu, M Kaya: 71(6):405 – 410
Ultrastructure: 71(6):405 – 410
Unal VS: see Dayican A
Unequal treatment: 71(5):314 – 321
Unfolded protein response: 71(5):289 – 297
Update in atherothrombotic disease, JF Viles-Gonzalez, SX Anand, C Valdiviezo, MU Zafar, R Hutter, J Sanz, T Rius, M Poon, V Fuster, JJ Badimon: 71(3):197 – 208
Uribarri J: see Vassalotti JA
Using community-based participatory research to reduce health disparities in East and Central Harlem, C Horowitz: 71(6):368 – 374
Utkan A: see Dayican A

Vaccination: 71(3):162 – 165
Vaccine: 71(2):86 – 93
Valdiviezo C: see Viles-Gonzalez JF
Valone DA, History of medical payments, a: continuity or crisis?: 71(4):219 – 224
Vasculitis: 71(5):330 – 334
Vassalotti JA, Falk A, Teodorescu V, Uribarri J, Multidisciplinary approach to hemodialysis vascular access at The Mount Sinai Hospital: 71(2):94 – 102
Vein mapping:71(2):94 – 102
Vein surgery: 71(1):42 – 46
Ventricular assist device: 71(1):47 – 54
Viles-Gonzalez JF, Anand SX, Valdiviezo C, Zafar MU, Hutter R, Sanz J, Rius T, Poon M, Fuster V, Badimon JJ, Update in atherothrombotic disease: 71(3):197 – 208
Vlachos A: see Sakorafas GH

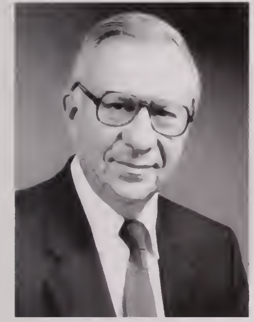
Walsh CE: see Chao H
Wang L-H, Molecular signaling regulating anchorage-independent growth of cancer cells: 71(6): 361 – 367
Wenger NS, Carmel S, Physicians' religiosity and end-of-life care attitudes and behaviors: 71(5):335 – 343
Where the wild things are: the power and challenge of adolescent group work, S Aronson: 71(3):174 – 180

Yesilova Z: see Iyisoy A

Zafar MU: see Viles-Gonzalez JF

In Memoriam

Ezra M. Greenspan, M.D.



Dr. Ezra Greenspan, Emeritus Clinical Professor of Medicine, died on September 3, 2004, after a long illness. He is survived by his wife Edith, his 3 children and 3 grandchildren. He was famed world-wide for publishing the first studies of combination chemotherapy for ovarian cancer in 1962 and for metastatic breast cancer in 1963.

After graduating from Cornell University in 1940, and New York University College of Medicine in 1943, he spent his entire professional career, except for military service, at Mount Sinai. His World War II assignment was in the U.S. Public Health Service, working for the National Cancer Institute in Baltimore, before the National Institutes of Health were consolidated in Bethesda.

Dr. Greenspan was a full member of the triumvirate, with Abraham Goldin and Emanuel Schoenbach, who conducted fundamental studies on aminopterin, the first drug reported to produce temporary remissions in acute leukemia of children. In 1950 and 1951, they completed important studies (including several on toxicity and combination therapies) that set the stage for treatment of human choriocarcinoma, the first human cancer cured by chemotherapy. Their pioneering research program was a keystone in the development of cancer chemotherapy for patients.

In 1952, Dr. Greenspan returned to Mount Sinai, where he built upon his earlier research collaboration. Armed with experimental preclinical data that combination chemotherapy, developed on an empiric basis, was effective in the mouse model, he carefully applied this to patients. A famous example was the safe use of oral low-dose methotrexate (until the earliest evidence for mucositis). For many years, Ezra was a “lone warrior” at Mount Sinai, bringing hope to legions of cancer patients and extending their lives. He also offered them his encouragement and enthusiasm, supplementing the chemotherapy regimens he was developing, with his own “holistic” approach to the disease.

Because his clinical research was contrary to accepted dogma, Dr. Greenspan had to overcome great bias and resistance. His before-and-after pictures of breast cancer metastasis in the lung, showing major regression, were published in *The Mount Sinai Journal of Medicine* in 1963. They had been rejected by another major journal because the reviewer insisted that the pictures must have been reversed. He wrote extensively on his clinical experience and laid the groundwork for international trials of combination chemotherapy, which subsequently corroborated his innovative approach.

In 1968 Dr. Greenspan established the Cancer Chemotherapy Foundation, which he served as chairman and medical director. The foundation, sustained in part by his grateful patients, has supported cancer research projects in all the medical schools of New York State. Its annual meetings attract nearly 2,000 attendees from all over the world. Dr. Greenspan, with extraordinary knowledge of research in progress, served as program chairman for these scientific feasts nearly up to the end of his life. In 2003 the attendees, apprehensive about his failing health, honored Dr. Greenspan with a citation:

Ezra M. Greenspan, M.D., Consummate Oncologist

> You pioneered the use of combination chemotherapy for patients with cancer. You shared your wisdom with generations of physicians over more than half a century. You educated a legion of oncologists through annual conferences on current and futuristic cancer therapies. You supported chemotherapeutic research with grants to intrepid investigators. You extended the lives of countless patients in your own practice and by your teachings in oncologic offices and clinics across the land. For your imagination, creativity, stalwart courage in the early days when you met nearly universal disbelief, for your tenacity, generosity of support, of spirit, and of self, you are held in reverential esteem. You have the thanks of those who have faced cancer as a personal challenge and of us gladiators, who have followed your leadership in waging battle.
>
> Hail, Ezra! We, who are about to succeed because you pointed the way, salute you.

James F. Holland, M.D.
Distinguished Professor of Neoplastic Diseases
and
Samuel Waxman, M.D.
Professor of Medicine
Mount Sinai School of Medicine

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